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(54) Title: PIPERAZINE DERIVATIVES AS HIV PROTEASE INHIBITORS

(57) Abstract

Oligopeptide analogs containing piperazine are described. These compounds are useful in the inhibition of HIV protease, the prevention or treatment of infection by HIV and the treatment of AIDS, either as compounds, pharmaceutically acceptable salts, pharmaceutical composition ingredients, whether or not in combination with other antivirals, immunomodulators, antibiotics or vaccines. Methods of treating AIDS and methods of preventing or treating infection by HIV are also described.

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TITLE OF THE INVENTION

PIPERAZINE DERIVATIVES AS HIV PROTEASE INHIBITORS

This application is a continuation-in-part of Merck Case 18882, Serial No. 08/017,090, filed February 12, 1992.

This application is related to Merck Case 18466, Serial No. 07/ 746,460, filed August 16, 1991; Merck Case 18583, Serial No. 07/781,470, filed October 13, 1991; and Merck Case 18583IA, Serial No. 07/929,991, filed August 21, 1992.

The present invention is concerned with compounds which inhibit the protease encoded by human immunodeficiency virus (HIV). The compounds, or pharmaceutically acceptable salts thereof, are of value in the prevention of infection by HIV, the treatment of infection by HIV and the treatment of the resulting acquired immune deficiency syndrome (AIDS).

The present invention also relates to pharmaceutical compositions containing the compounds and to a method of use of the present compounds and other agents for the treatment of AIDS & viral infection by HIV.

BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV. A common feature of retrovirus replication is the extensive post-translational processing of precursor polyproteins by a virally encoded protease to generate mature viral proteins required for virus assembly and function. Inhibition of this processing prevents the production of normally infectious virus. For example, Kohl, N.E., et. al., Proc. Natl. Acad. Sci. USA, 85, 4686 (1988), demonstrated that genetic inactivation of the HIV encoded protease resulted in the production of immature, non-infectious virus particles. These results

indicate that inhibition of the HIV protease represents a viable method for the treatment of AIDS and the prevention or treatment of infection by HIV.

Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner, L. et al., Nature, 313, 277(1985)]. Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, an endonuclease and an HIV protease [Toh, H. et al., EMBO J. 4, 1267 (1985); Power, M.D. et al., Science, 231, 1567 (1986); Pearl, L.H. et al., Nature 329, 351 (1987)]. Applicants demonstrate that the compounds of this invention are inhibitors of HIV protease.

Related art includes Hoffman-LaRoche EPO applications. EPO 389898, EPO 346847, and EPO 432695 each disclose HIV protease inhibitors but the compounds are substantially different because they have an amino acid (or analog thereof) attached to the amino-terminal end of the transition state analog. EPO 432694 discloses synthetic intermediates which are different from the compounds of the present invention.

The compounds of the present invention contain piperazine with one or more basic amines. The particular advantages of these compounds are increased oral bioavailability, enhanced water solubility, and decreased serum protein binding.

BRIEF DESCRIPTION OF THE INVENTION

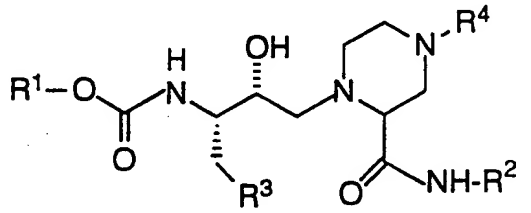
Compounds of formula I, as herein defined, are disclosed. These compounds are useful in the inhibition of HIV protease, the prevention of infection by HIV, the treatment of infection by HIV and in the treatment of AIDS, either as compounds, pharmaceutically acceptable salts, hydrates or esters, pharmaceutical composition ingredients, whether or not in combination with other antivirals, immunomodulators, antibiotics or vaccines. Methods of treating AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV are also disclosed.

ABBREVIATIONS

	Activating Agent
HBT (HOBT or HOBt)	1-hydroxybenzotriazole hydrate
	Condensing Agent
EDC	1-ethyl-3-(3-dimethylamino-propyl)carbodiimide

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

This invention is concerned with the compounds of Formula I, combinations thereof, or pharmaceutically acceptable salts thereof, in the inhibition of HIV protease, the prevention of infection by HIV, the treatment of infection by HIV and in the treatment of the resulting acquired immune deficiency syndrome (AIDS). Compounds of formula I are defined as follows:



(I)

wherein:

R^1 is

a) 5- to 7- membered carbocylic ring which is either saturated, partially saturated or unsaturated, the carbocylic ring being unsubstituted or substituted with one or more of C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-3} alkoxy, halo-C_{1-3} alkyl, aryl-C_{1-3} alkyl, or C_{3-5} cycloalkyl; or

b) 5- to 7-membered heterocycle having one heteroatom selected from O or S, any of which heterocycle is unsubstituted or substituted with one or more of

C_{1-4} alkyl, C_{2-4} alkenyl, oxo, C_{3-5} cycloalkyl, or C_{1-3} alkoxy;

R^2 is

a) C_{1-5} alkyl, unsubstituted or substituted with one or more of -OH or C_{1-3} alkoxy; or

b) 5- to 7-membered carbocyclic ring which is either saturated, partially saturated or unsaturated, the carbocyclic ring being unsubstituted or substituted with one or more of C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-3} alkoxy, or hydroxy;

R^3 is

a) Phenyl unsubstituted or substituted with one or more of -OH or C_{1-3} alkoxy; or

b) C_{5-7} cycloalkyl, unsubstituted or substituted with one or more of -OH or C_{1-3} alkoxy,

R^4 is

a) -V-R^5; wherein V is absent, -C(O)-Q-, or -SO_2-Q-; and wherein Q is absent, -O-, -NH-, or 5- to 7-membered heterocycle, which heterocycle is unsubstituted or substituted with one or more of -C_{1-4}alkyl, oxo, or halo;

b) 5- to 7-membered heterocycle, unsubstituted or substituted with one or more of -C_{1-4}alkyl or halo; or

c) C_{1-4}alkenyl, unsubstituted or substituted once with aryl or heterocycle;

d) C_{3-5}cycloalkyl, unsubstituted or substituted at the 3-position with C_{1-4}alkyl;

R^5 is a) hydrogen, or

b) -C_{1-4}alkyl unsubstituted or substituted with one or more of
   i) halo,
   ii) hydroxy,
   iii) C_{1-3} alkoxy,
   iv) aryl unsubstituted or substituted with one or more of C_{1-4}alkyl, C_{1-4}alkoxy, nitro, amino, amido, carboxy, hydroxy, halo or aryl;
   v) -W-aryl or W-benzyl, wherein W is -O-, -S-, or -NH-; or
   vi) heterocycle, unsubstituted or substituted with one or more of C_{1-4}alkyl, hydroxy or halo;
   vii) carboxyl;

c) -C_{3-5}cycloalkyl, unsubstituted or substituted at the 3-position with C_{1-4}alkyl;

or a pharmaceutically acceptable salt or hydrate thereof.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures and as individual diastereomers or enantiomers, with all isomeric forms being included in the present invention.

When any variable (e.g., heterocycle, R^1 or R^2, etc.) occurs more than one time in any constituent or in formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein except where noted, "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms (Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl); "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Alkenyl" is intended to include a hydrocarbon chain of

either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, and the like. "Halo", as used herein, means fluoro, chloro, bromo or iodo.

As used herein, with exceptions as noted, "aryl" is intended to mean phenyl (Ph) or naphthyl. "Carbocyclic" is intended to mean any stable 5- to 7-membered carbon ring or 7- to 10-membered bicyclic carbon ring, any of which may be saturated or partially unsaturated.

The term heterocycle or heterocyclic, as used herein except where noted, represents a stable 5- to 7-membered mono- or bicyclic or stable 7- to 10-membered bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazoyl, benzopyranyl, benzothiopyranyl, tetrahydrofuryl, tetrahydropyranyl, and tetrahydrothienyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone and isobenzothiopyranyl.

The pharmaceutically-acceptable salts of the compounds of Formula I (in the form of water- or oil-soluble or dispersible products) include the conventional non-toxic salts or the quaternary ammonium salts of these compounds, which are formed, e.g., from inorganic or organic acids. Examples of such acid addition salts include acetate,

adipate, alginate, aspartate, benzoate, bisulfate, citrate, digluconate, dodecylsulfate, fumarate, glycerophosphate, hemisulfate, hydrochloride, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, succinate and tartrate.

One preferred embodiment of this invention is compounds of Formula I, wherein

R^1 is a 5- to 7-membered heterocycle having one heteroatom selected from 0 or S, any of which heterocycle is unsubstituted or substituted with one or more of C_{1-4} alkyl, C_{2-4} alkenyl, oxo, or C_{1-3} alkoxy;

R^2 is C_{1-5} alkyl, unsubstituted or substituted with one or more of -OH;

R^3 is phenyl unsubstituted or substituted once with -OH or C_{1-3} alkoxy;

R^4 is

a) -V-R^5; wherein V is absent or -SO_2-Q-; and wherein Q is absent or a 5- to 7-membered heterocycle, which heterocycle is unsubstituted or substituted with one or more of -C_{1-4}alkyl or halo; or

b) 5- to 7-membered heterocycle, unsubstituted or substituted with one or more of -C_{1-4}alkyl or halo;

c) -C_{3-5}cycloalkyl, unsubstituted or substituted at the 3-position with C_{1-4}alkyl;

R^5 is -C_{1-4} alkyl unsubstituted or substituted with one or more of

i) aryl unsubstituted or substituted with one or more of C_{1-4} alkyl, hydroxy, halo or aryl; or

ii) heterocycle unsubstituted or substituted with one or more of C_{1-4} alkyl, hydroxy, or halo.

A third embodiment is further limited to compounds wherein:

R^1 is 1,1-dioxo-tetrahydrothienyl or tetrahydrofuranyl, either of which is unsubstituted or substituted with C_{1-4} alkyl, C_{2-4} alkenyl or C_{1-3} alkoxy;

R^2 is t-butyl or 2-methylpropyl;

R^3 is phenyl;

R^4 is
a) -V-R^5, wherein V is absent; or
b) 5- to 7- membered heterocycle, unsubstituted or substituted with one or more of -C_{1-4} alkyl or halo.

A fourth embodiment is further limited to compound wherein:

R^1 is tetrahydrofuran-3-yl; or, 1,1-dioxo-tetrahydrothien-3-yl, unsubstituted or substituted with methyl, ethyl, n-propyl, i-propyl, methoxy, ethoxy, or propenyl.

In a fifth embodiment, compounds of Formula I are limited to those wherein:

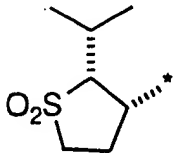
R^1 is a 5- to 7-membered heterocycle having one S heteroatom, said heterocycle unsubstituted or substituted with one or more of C_{1-4} alkyl, oxo or C_{3-5} cycloalkyl;
R^2 is C_{1-5} alkyl;
R^3 is phenyl.

A sixth embodiment is further limited to:

R^1 is 1,1-dioxotetrahydrothien-3-yl, unsubstituted or substituted with C_{1-4} alkyl, or C_{3-5} cycloalkyl;

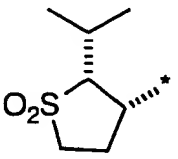
R^2 is C_{1-5} alkyl;
R^3 is phenyl.

In a seventh embodiment, compounds of Formula I are limited to those wherein:
R^1 is



; wherein the asterisk indicates the point of attachment;
R^2 is t-butyl;
R^3 is phenyl;
R^4 is 4-pyridylmethyl, unsubstituted or substituted at the 2-position with methyl, ethyl, propyl, butyl or isobutyl; C_{3-5} cycloalkyl methyl, unsubstituted or substituted once at the 3-position either with C_{1-4}alkyl.

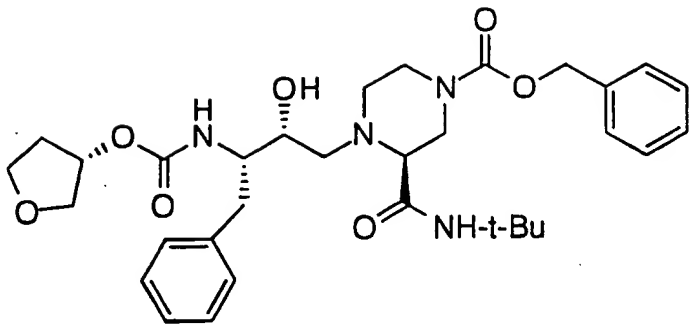
In an eighth embodiment, compounds of Formula I are limited to those wherein:
R^1 is



; wherein the asterisk indicates the point of attachment;
R^2 is t-butyl;
R^3 is phenyl;
R^4 is methyl, unsubstituted once with imidazopyrazinyl, oxazolopyridinyl, imidazopyridinyl, purinyl, or methylpurinyl.

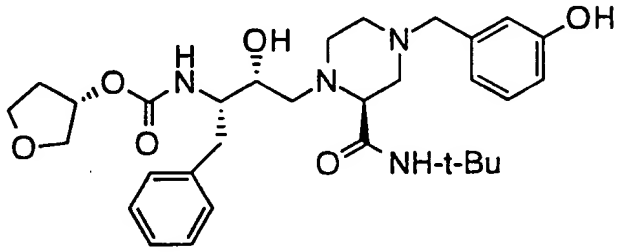
Most preferred compounds of this invention include the following:

Compound A:



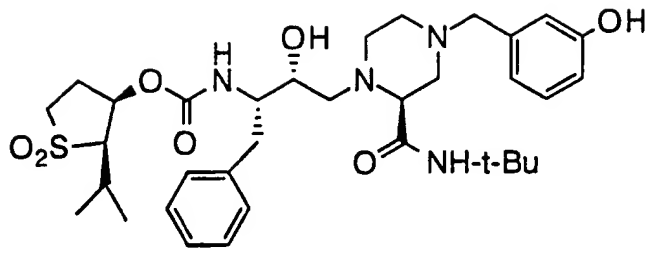
N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(S)-tetrahydrofuranyloxycarbonylamino]-butyl]-4-(benzyl-oxycarbonyl)piperazinyl-2(S)-carboxamide; or

Compound B:



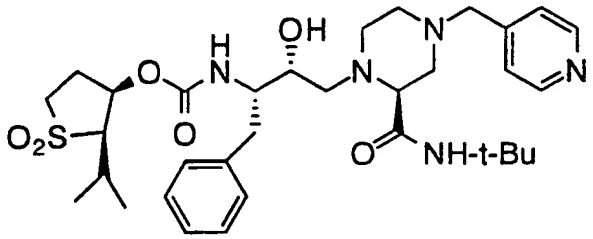
N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(S)-tetrahydrofuranyloxycarbonylamino]-butyl]-4-(3'-hydroxy-phenylmethyl)piperazinyl-2(S)-carboxamide; or

Compound C:



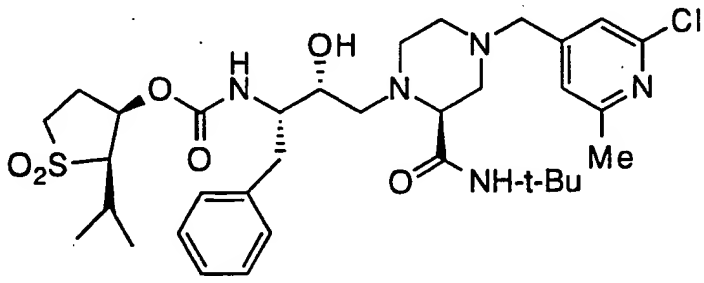
N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxycarbonylamino]butyl]-4-(3'-hydroxyphenylmethyl)piperazine-2(S)-carboxamide;

Compound D:



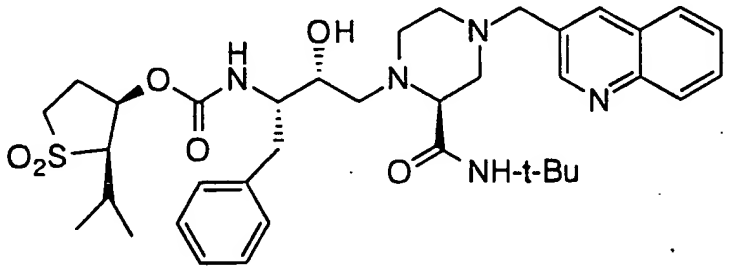
N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxycarbonylamino]butyl]-4-(4'-pyridylmethyl)piperazine-2(S)-carboxamide;

Compound E:



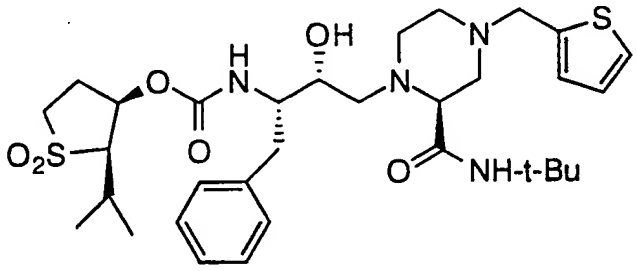
N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxycarbonylamino]butyl]-4-[4'-(2"-chloro-6"-methyl)pyridylmethyl]piperazine-2(S)-carboxamide;

Compound F:



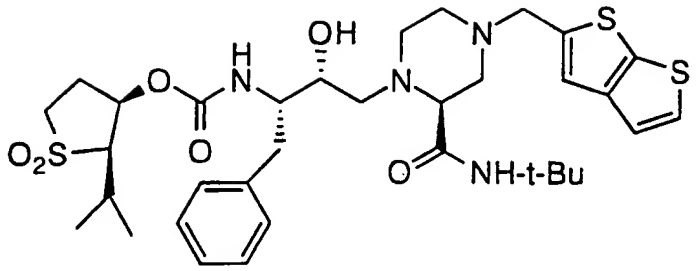
N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxycarbonylamino]butyl]-4-(3'-quinolinylmethyl]piperazine-2(S)-carboxamide;

Compound G:



N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxycarbonylamino]butyl]-4-(2'-thienylmethyl)piperazine-2(S)-carboxamide;

Compound H:

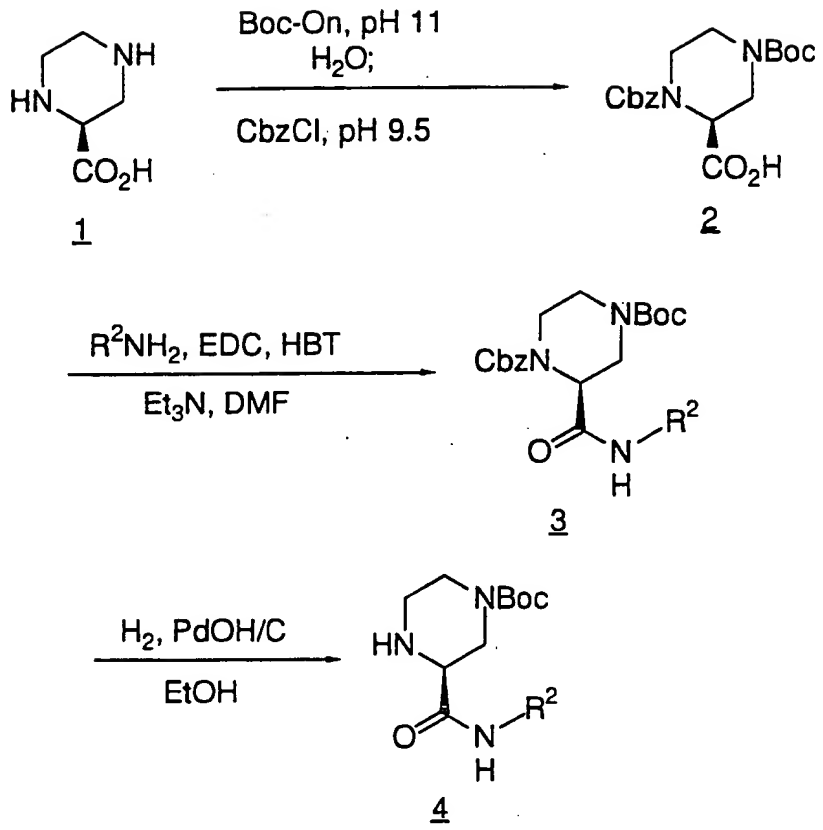


N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1'",1'"-dioxo-2'"(R)-methylethyl]tetrahydrothienyloxycarbonylamino]butyl]-4-(2'-thieno[2,3-b]thienylmethyl)piperazine-2(S)-carboxamide;

or pharmaceutically acceptable salt thereof.

The compounds of the present invention are prepared in accordance with Schemes I-IV.

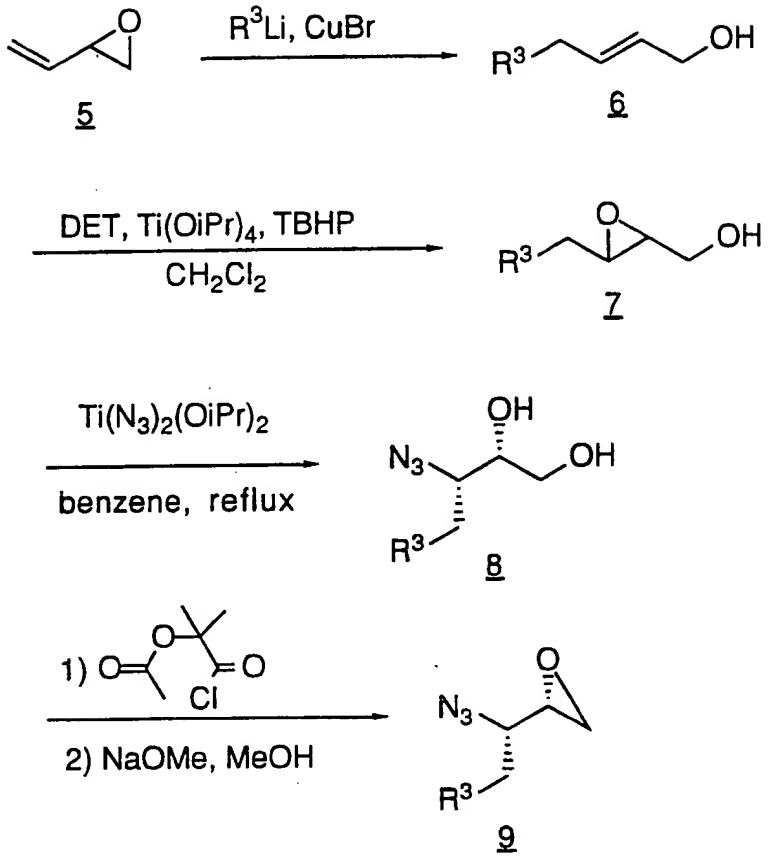
SCHEME I



1 2 3 4

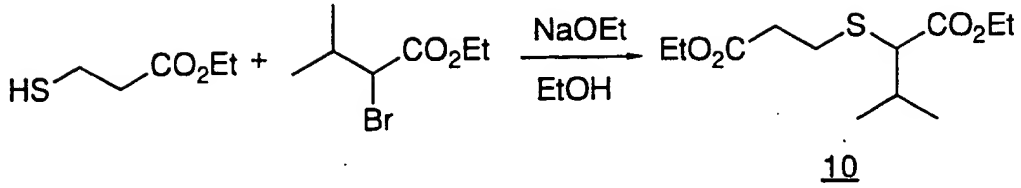
Compound 2 is prepared by the procedure of Bigge, C.F. et al., Tetrahedron Lett., 30, 5193 (1989); starting with 2(S)-piperazinecarboxylic acid. [See also Felder, E. et al. Helv. Chim. Acta, 117, 888 (1960]. Coupling of the acid 2 with t-butylamine under the effect of HOBt and EDC provides the t-butylamide 3, which, upon hydrogenation, is converted to the amine 4. Example 1 illustrates but does not limit Scheme 1.

SCHEME II



Catalytic asymmetric or Sharpless epoxidation of the allylic alcohol 6 to produce 7 is performed by the methods of Gao, Y. et al., J. Am. Chem. Soc. 109, 5765 (1987). Regio-selective azide opening of the 2,3-epoxy alcohol 7 to give 8 is facilitated by titanium according to Caron, M. et al., J. Org. Chem. 53, 5185 (1988). Example 2 illustrates but does not limit Scheme II.

Scheme III



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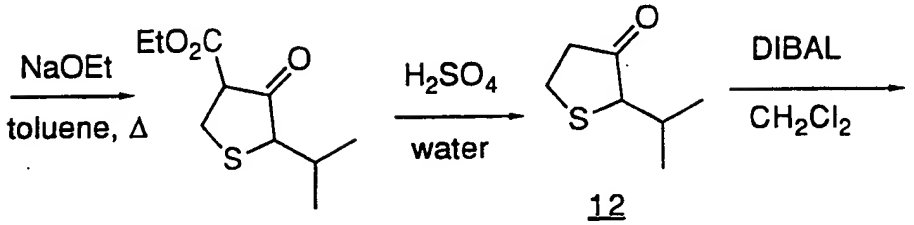

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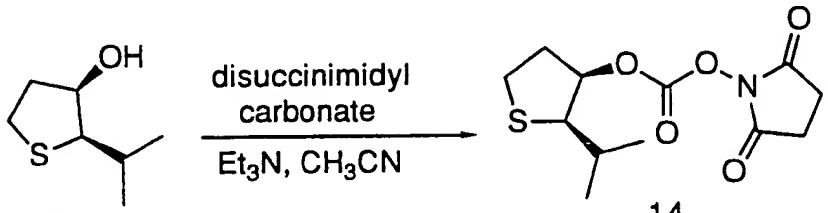
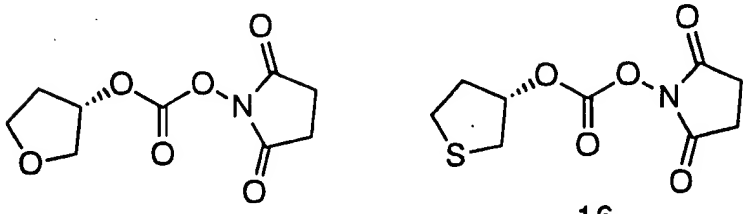


13 14

2(R,S), 3(R,S) 2(R,S), 3(R,S)

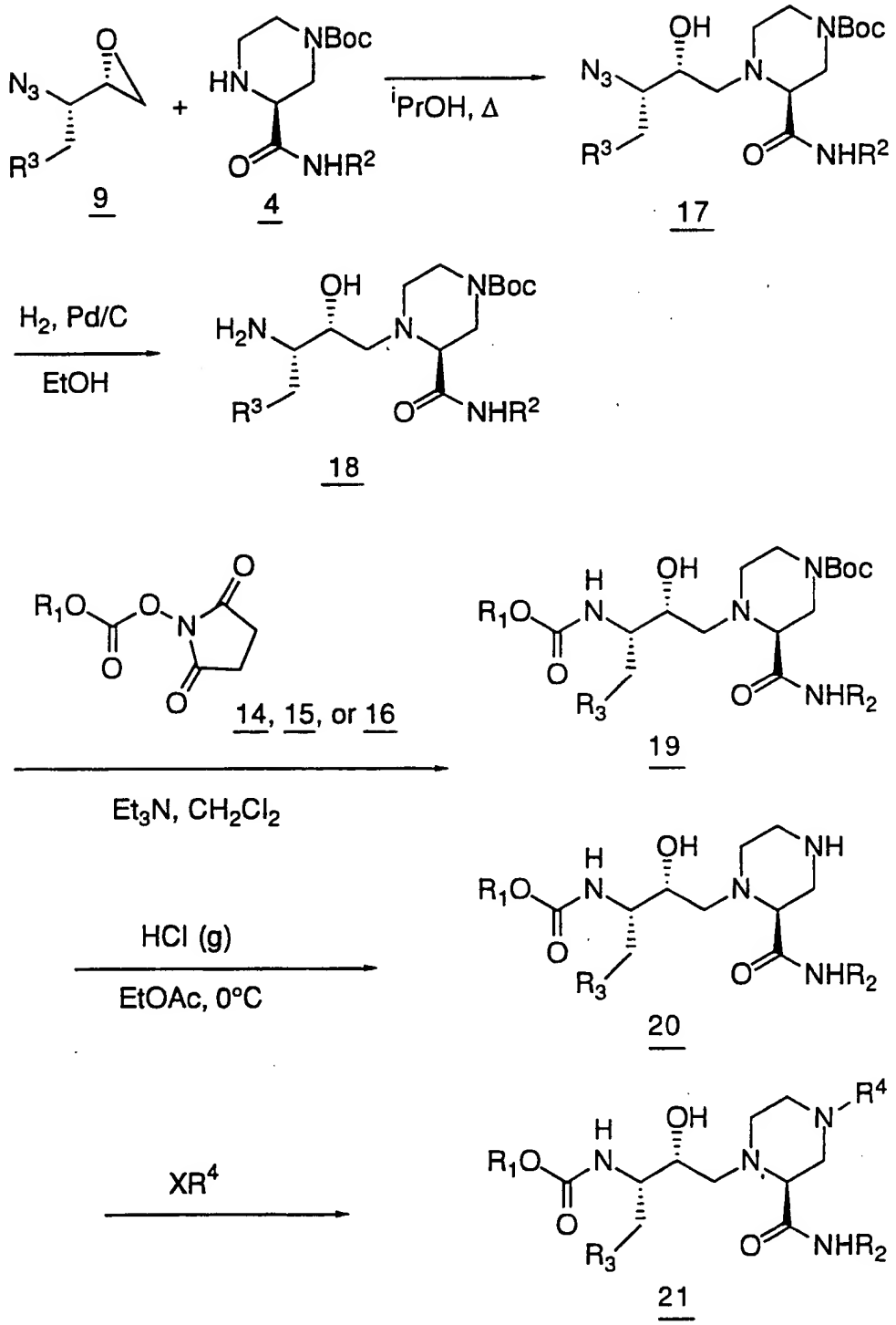


15 16

The coupling reaction of ethyl 3-mercaptopropionate and ethyl 2-bromo-3-methylbutanoate furnishes compound 10 which is cyclized under Dieckman conditions to give the keto ester 11. Hydrolytic decarboxylation of 11 by H_2SO_4 followed by selective reduction of the ketone 12 yields the alcohol 13 which is converted to

the mixed carbonate 14 using disuccinimidyl carbonate in the presence of a base, e.g. triethylamine. Compounds 15 and 16 are made by reacting the corresponding alcohols with disuccinimidyl carbonate. Examples 3-6 illustrate but do not limit Scheme III.

SCHEME IV

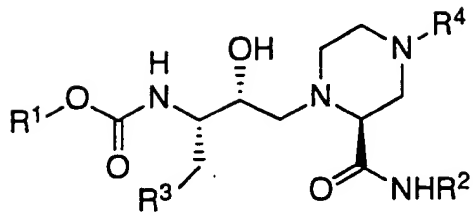

N3
R3
9
HN
NBoc
O
NHR2
4
iPrOH, Δ
OH
17
H2, Pd/C
EtOH
H2N
18
R1O
14, 15, or 16
Et3N, CH2Cl2
R3
19
HCl (g)
EtOAc, 0°C
NH
20
XR4
R4
21

Condensation of the azide epoxide 9 with the piperazine intermediate 4 is performed by, for example, heating a mixture in refluxing isopropanol, to give the azido-alcohol 17 in good yield. Reduction over palladium on carbon yields the amine 18, which is then reacted with the appropriate N-substituted succinimide 14, 15, or 16 in the presence of, e.g., TEA, to give compound 19. In the case of coupling with 14 or 16, the sulfide groups are selectively oxidized by catalytic amount of OsO_4 and stoichiometric amount of N-methyl-morpholine N-oxide (NMO). Isomers are separated in the case of coupling with 14. Then the protecting Boc group is removed by acid treatment and the subsequent free amine is coupled to the substituents through alkylation, reductive amination, or amidation. Examples 7-17 illustrate but do not limit Scheme IV.

Other substituents for R^2 and R^3 in Formula I are readily prepared by those skilled in the art, by substituting and/or protecting appropriate groups in the schemes outlined above.

The compounds of the present invention include but are not limited to those of the following Tables 1 and 2:

TABLE 1



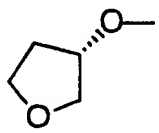
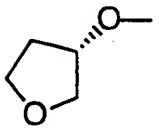
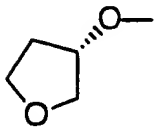
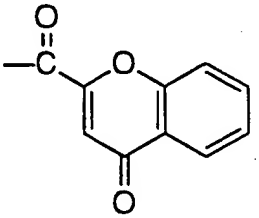
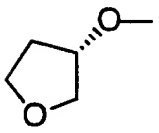
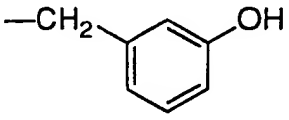
R^1O-	R^2	R^3	R^4
	$-C(CH_3)_3$	-Ph	$-COOCH_2Ph$
	$-C(CH_3)_3$	-Ph	$-COOC(CH_3)_3$
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	

Table 1 (continued)

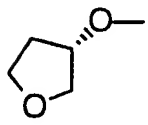
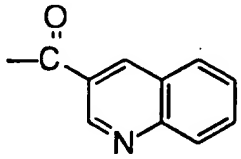
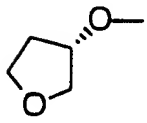
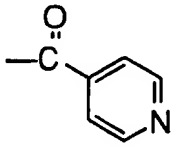
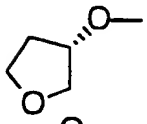
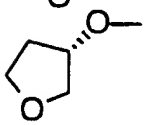
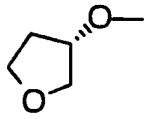
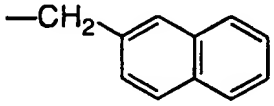
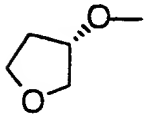
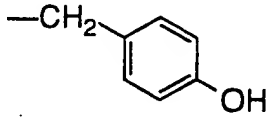
R^1O-	R^2	R^3	R^4
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	$-CH_2CH_2CH_2Ph$
	$-C(CH_3)_3$	-Ph	$-CH_2Ph$
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	

Table 1 (continued)

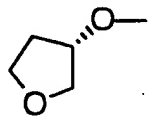
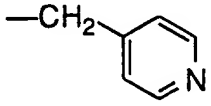
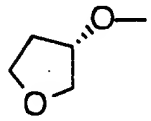
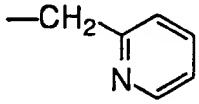
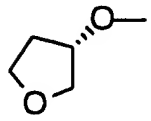
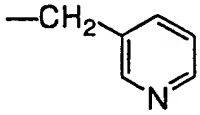
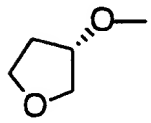
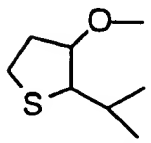
R^1O-	R^2	R^3	R^4
	-$C(CH_3)_3$	-Ph	
	-$C(CH_3)_3$	-Ph	
	-$C(CH_3)_3$	-Ph	
	-$C(CH_3)_3$	-Ph	-CH_2CH_2Ph
 (2S,R; 3S,R)	-$C(CH_3)_3$	-Ph	-$COOC(CH_3)_3$

Table 1 (continued)

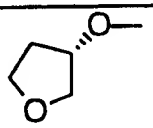
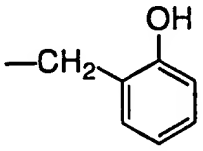
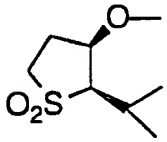
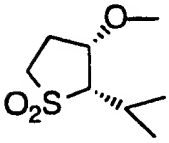
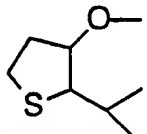
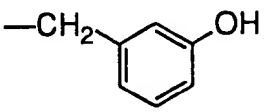
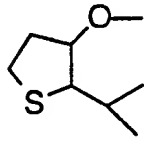
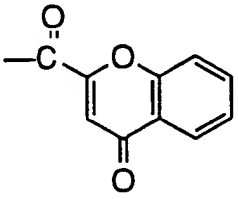
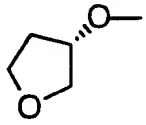
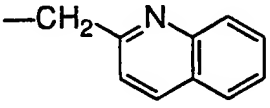
R^1O-	R^2	R^3	R^4
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	$-COOC(CH_3)_3$
	$-C(CH_3)_3$	-Ph	$-COOC(CH_3)_3$
 (2S,R; 3S,R)	$-C(CH_3)_3$	-Ph	
 (2S,R; 3S,R)	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	

Table 1 (continued)

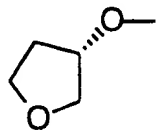
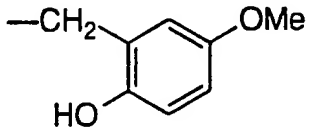
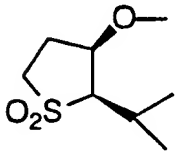
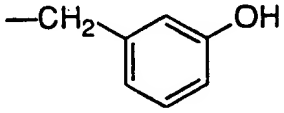
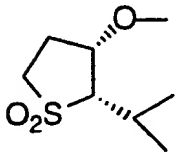
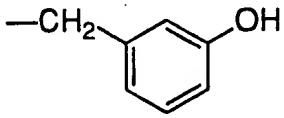
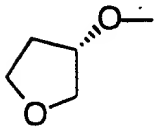
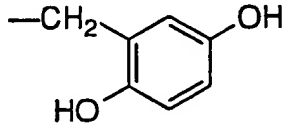
R^1O-	R^2	R^3	R^4
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	

Table 1 (continued)

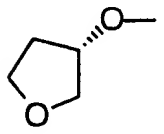
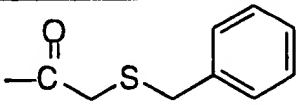
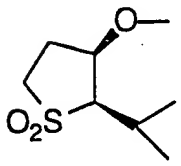
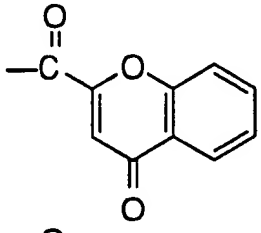
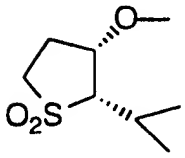
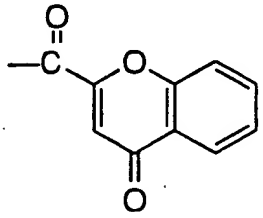
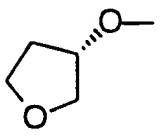
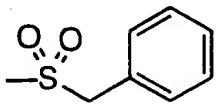
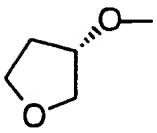
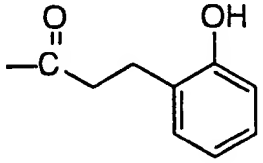
R^1O-	R^2	R^3	R^4
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	

Table 1 (continued)

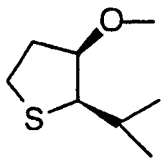
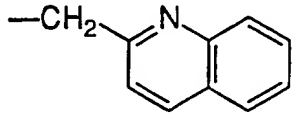
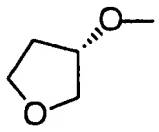
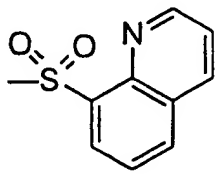
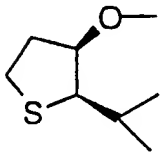
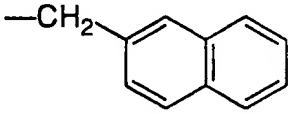
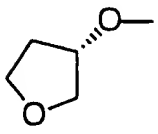
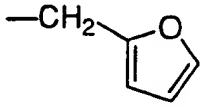
R^1O-	R^2	R^3	R^4
 (2S,R; 3S,R)	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	
 (2S,R; 3S,R)	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	

Table 1 (continued)

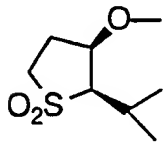
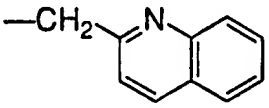
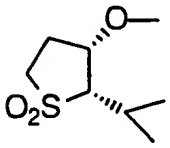
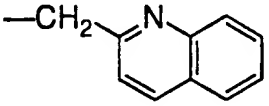
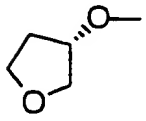
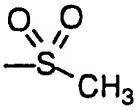
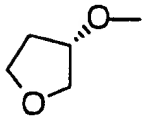
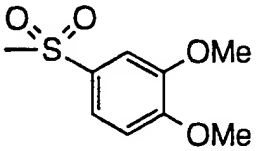
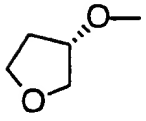
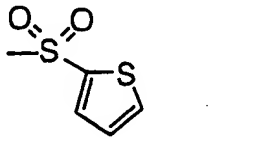
R^1O-	R^2	R^3	R^4
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	

Table 1 (continued)

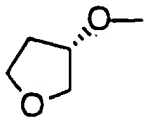
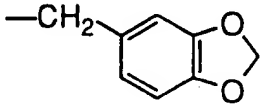
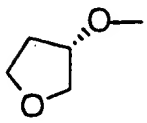
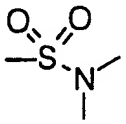
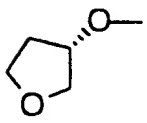
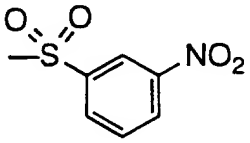
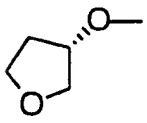
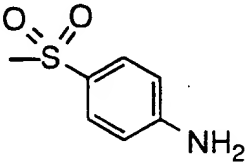
R^1O-	R^2	R^3	R^4
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	

Table 1 (continued)

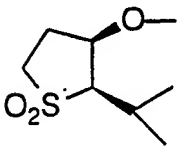
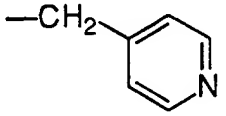
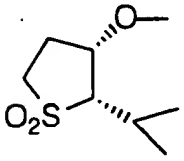
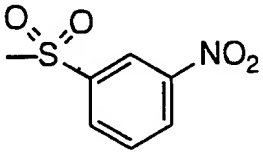
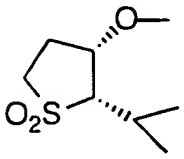
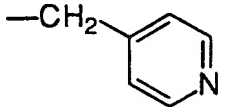
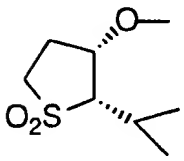
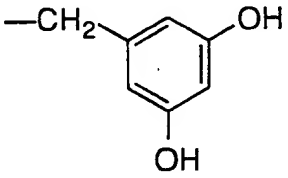
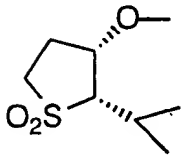
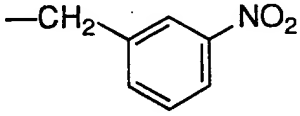
R^1O-	R^2	R^3	R^4
	-$C(CH_3)_3$	-Ph	
	-$C(CH_3)_3$	-Ph	
	-$C(CH_3)_3$	-Ph	
	-$C(CH_3)_3$	-Ph	
	-$C(CH_3)_3$	-Ph	

Table 1 (continued)

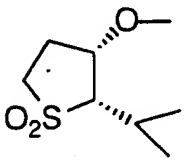
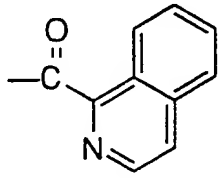
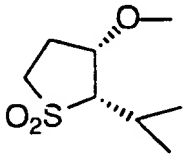
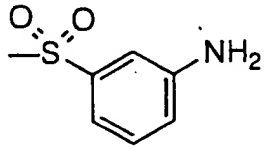
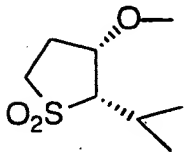
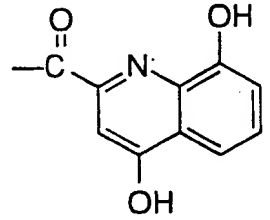
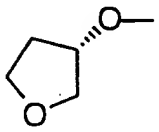
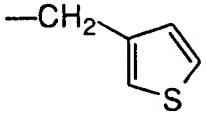
R^1O-	R^2	R^3	R^4
	-$C(CH_3)_3$	-Ph	
	-$C(CH_3)_3$	-Ph	
	-$C(CH_3)_3$	-Ph	
	-$C(CH_3)_3$	-Ph	

Table 1 (continued)

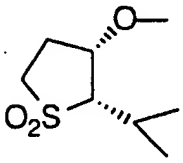
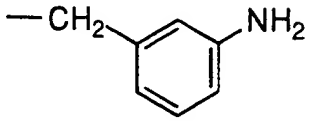
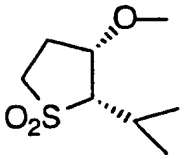
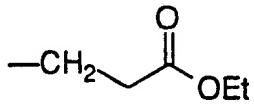
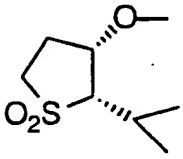
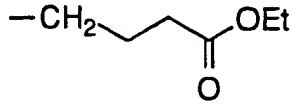
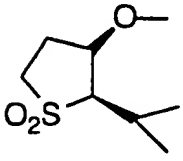
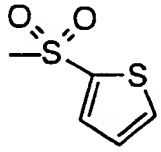
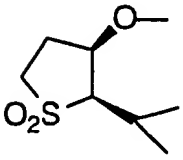
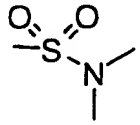
R^1O-	R^2	R^3	R^4
	-$C(CH_3)_3$	-Ph	
	-$C(CH_3)_3$	-Ph	
	-$C(CH_3)_3$	-Ph	
	-$C(CH_3)_3$	-Ph	
	-$C(CH_3)_3$	-Ph	

Table 1 (continued)

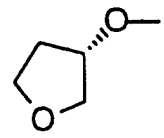
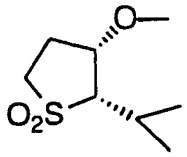
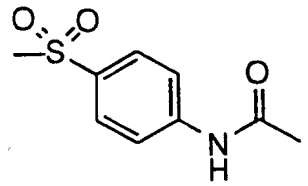
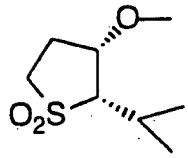
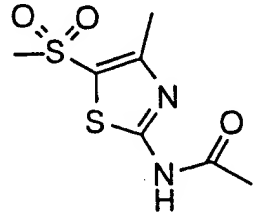
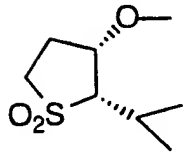
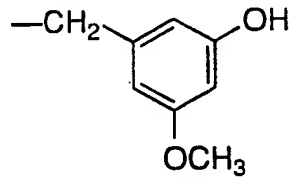
R^1O-	R^2	R^3	R^4
	-$CH(CH_3)_2$	-Ph	-$COOCH_2Ph$
	-$C(CH_3)_3$	-Ph	
	-$C(CH_3)_3$	-Ph	
	-$C(CH_3)_3$	-Ph	

Table 1 (continued)

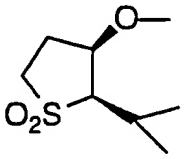
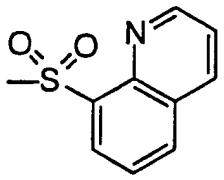
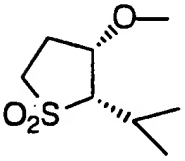
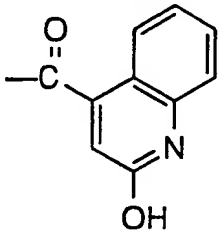
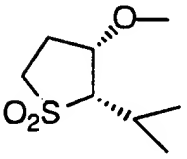
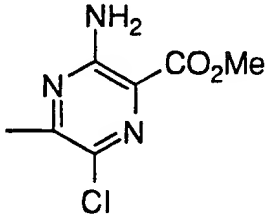
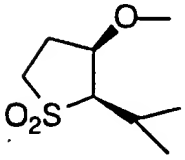
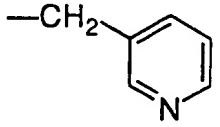
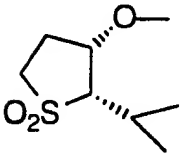
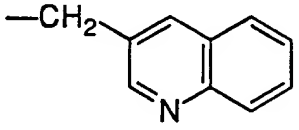
R^1O-	R^2	R^3	R^4
	-C(CH$_3$)$_3$	-Ph	
	-C(CH$_3$)$_3$	-Ph	
	-C(CH$_3$)$_3$	-Ph	
	-C(CH$_3$)$_3$	-Ph	
	-C(CH$_3$)$_3$	-Ph	

Table 1 (continued)

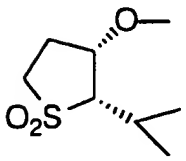
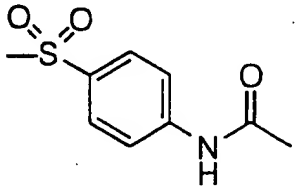
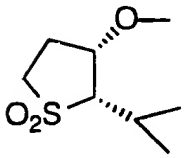
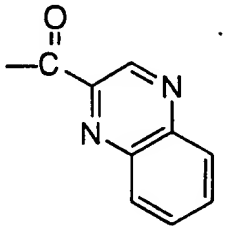
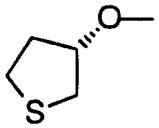
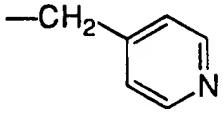
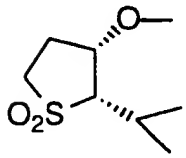
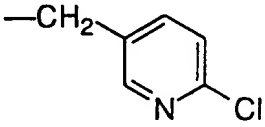
R^1O-	R^2	R^3	R^4
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	

Table 1 (continued)

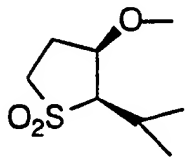
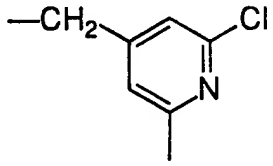
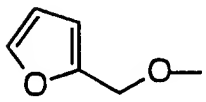
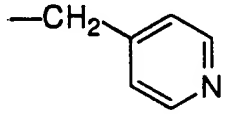
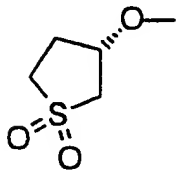
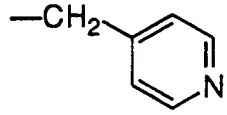
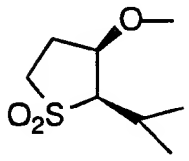
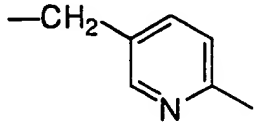
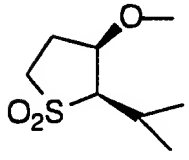
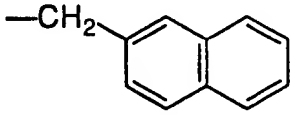
R^1O-	R^2	R^3	R^4
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	

Table 1 (continued)

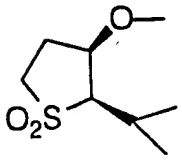
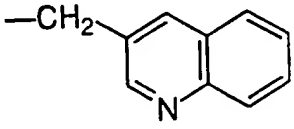
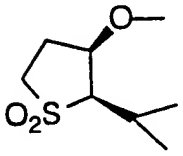
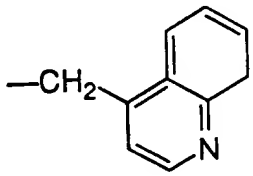
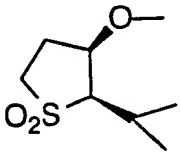
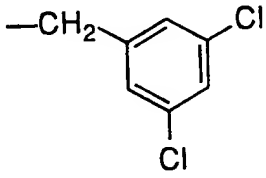
R^1O-	R^2	R^3	R^4
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	
	$-C(CH_3)_3$	-Ph	

Table 1 (continued)

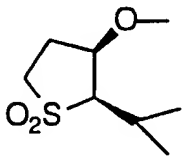
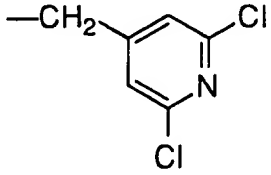
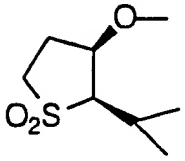
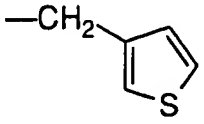
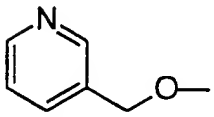
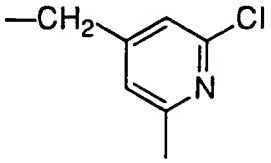
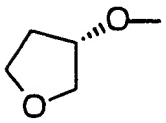
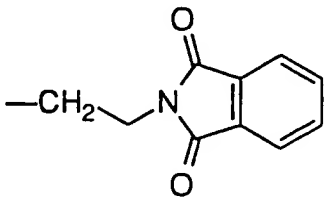
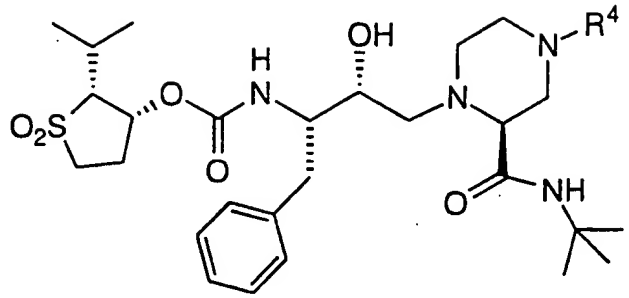
R^1O-	R^2	R^3	R^4
	-$C(CH_3)_3$	-Ph	
	-$C(CH_3)_3$	-Ph	
	-$C(CH_3)_3$	-Ph	
	-$C(CH_3)_3$	-Ph	

TABLE 2



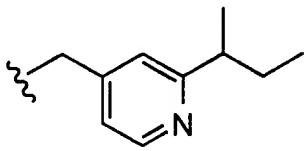
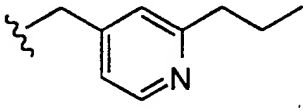
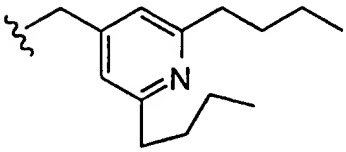
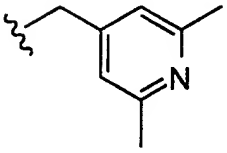
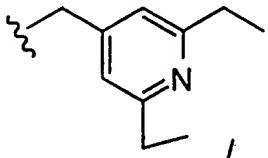
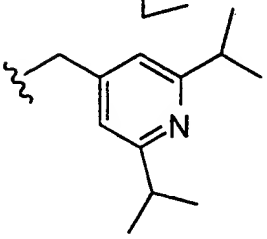
R^4	MP°C
	90-94
	81-88
	80-88
	98-105
	103-106
	94-98

Table 2 (continued)

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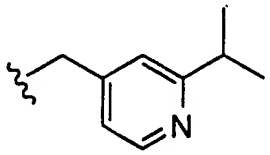
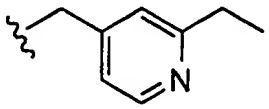
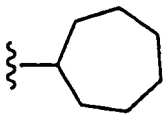
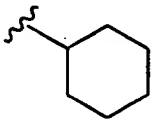
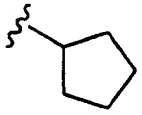
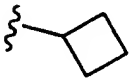
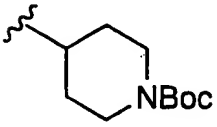
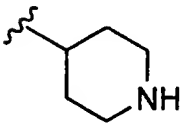
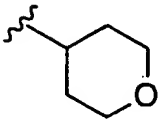
	92-99
	101-108
	94-100
	99-104
	98-103
	97-101
	117-119
	
	109-114

Table 2 (continued)

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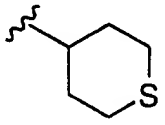
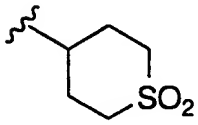
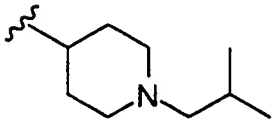
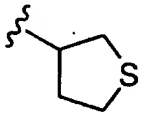
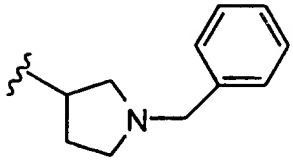
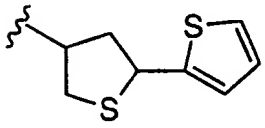
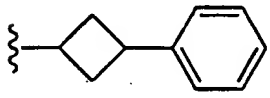
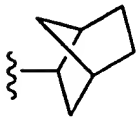
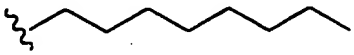
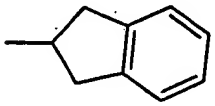
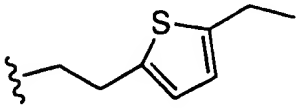
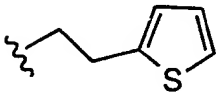
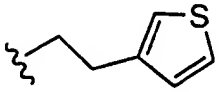
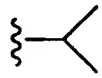
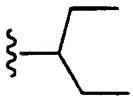
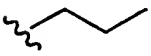
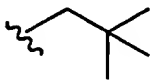
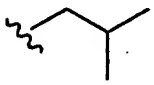
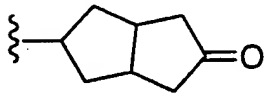
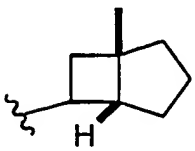
	108-111
	132-134
	84-88
	136-142
	83-89
	99-108
	96-104
	114-119

Table 2 (continued)

R^4	MP°C
	117-121
	102-110
	96-99
	103-106
	82-86
	93-98
	92-95
	82-88
	95.5-102
	91-96
	108-112
	

The last step in the synthesis of the compounds of Table 2 involves substitution of the N4 position of the piperazine. This step is conveniently carried out by the principles and practice illustrated in Examples 18 and 19.

The compounds of the present invention are useful in the inhibition of HIV protease, the prevention or treatment of infection by the human immunodeficiency virus (HIV) and the treatment of consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by e.g., blood transfusion, accidental needle stick, or exposure to patient blood during surgery.

The compounds of this invention are also useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to HIV protease, e.g., by competitive inhibition. Thus the compounds of this invention are commercial products to be sold for these purposes.

For these purposes, the compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

Thus, in accordance with the present invention there is further provided a method of treating and a pharmaceutical composition for treating HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically-

effective amount of a compound of the present invention, or a pharmaceutically-acceptable salt thereof.

These pharmaceutical compositions may be in the form of orally-administrable suspensions or tablets; nasal sprays; sterile injectable preparations, for example, as sterile injectable aqueous or oleagenous suspensions or suppositories.

When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, these compositions may be prepared by mixing the drug with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquidify and/or dissolve in the rectal cavity to release the drug.

Dosage levels of the order of 0.02 to 5.0 or 10.0 grams-per-day are useful in the treatment or prevention of the above-indicated conditions, with oral doses two-to-five times higher. For example, infection by HIV is effectively treated by the administration of from 10 to 50 milligrams of the compound per kilogram of body weight from one to three times per day. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age of the patient, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

The present invention is also directed to combinations of the HIV protease inhibitory compounds with one or more agents useful in the treatment of AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators, anti-infectives, or vaccines known to those of ordinary skill in the art.

TABLE C

ANTIVIRALS

Drug Name	Manufacturer	Indication
AL-721	Ethigen (Los Angeles, CA)	ARC, PGL HIV positive, AIDS
Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
Acemannan	Carrington Labs (Irving, TX)	ARC (See also immunomodulators)
Cytovene	Syntex	sight threatening CMV
Ganciclovir	(Palo Alto, CA)	peripheral CMV retinitis
d4T Didehydrodeoxy-thymidine	Bristol-Myers (New York, NY)	AIDS, ARC
ddI Dideoxyinosine	Bristol-Myers (New York, NY)	AIDS, ARC
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection (See also immunomodulators)

Drug Name	Manufacturer	Indication
Trisodium Phosphonoformate	Astra Pharm. Products, Inc (Westborough, MA)	CMV retinitis, HIV infection, other CMV infections
Dideoxycytidine; ddC	Hoffman-La Roche (Nutley, NJ)	AIDS, ARC
Novapren	Novaferon Labs, Inc. (Akron, OH) Diapren, Inc. (Roseville, MN, marketer)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Zidovudine; AZT AIDS, adv, ARC	Burroughs Wellcome (Rsch. Triangle Park, NC)	AIDS, adv, ARC pediatric AIDS, Kaposi's sarcoma, asymptomatic HIV infection, less severe HIV disease, neurological involvement, in combination with other therapies.
Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC

Drug Name	Manufacturer	Indication
Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
Alpha Interferon	Burroughs Wellcome (Rsch. Triangle Park, NC)	Kaposi's sarcoma, HIV in combination w/Retrovir
Acyclovir	Burroughs Wellcome	AIDS, ARC, asymptomatic HIV positive, in combination with AZT.
Antibody which neutralizes pH labile alpha aberrant Interferon in an immuno-adsorption column	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC

Drug Name	Manufacturer	Indication
L-697,661	Merck (Rahway, NJ)	AIDS, ARC, asymptomatic HIV positive, also in combination with AZT.
L-696,229	Merck (Rahway, NJ)	AIDS, ARC, asymptomatic HIV positive, also in combination with AZT.

IMMUNO-MODULATORS

Drug Name	Manufacturer	Indication
AS-101	Wyeth-Ayerst Labs. (Philadelphia, PA)	AIDS
Bropirimine	Upjohn (Kalamazoo, MI)	advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC (See also anti-virals)

Drug Name	Manufacturer	Indication
CL246,738	American Cyanamid (Pearl River, NY) Lederle Labs (Wayne, NJ)	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection (See also anti-virals)
Gamma Interferon	Genentech (S. San Francisco, CA)	ARC, in combination w/TNF (tumor necrosis factor)
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute (Cambridge, MA) Sandoz (East Hanover, NJ)	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Hoeschst-Roussel (Sommerville, NJ) Immunex (Seattle, WA)	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough (Madison, NJ)	AIDS, in combination w/AZT

Drug Name	Manufacturer	Indication
HIV Core Particle Immunostimulant	Rorer (Ft. Washington, PA)	seropositive HIV
IL-2 Interleukin-2	Cetus (Emeryville, CA)	AIDS, in combination w/AZT
IL-2 Interleukin-2	Hoffman-La Roche (Nutley, NJ) Immunex	AIDS, ARC, HIV, in combination w/AZT
Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute (Miami, FL)	AIDS, ARC
Alpha-2 Interferon	Schering Plough (Madison, NJ)	Kaposi's sarcoma w/AZT: AIDS

Drug Name	Manufacturer	Indication
Methionine-Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp. (Summit, NJ)	Kaposi's sarcoma
Granulocyte Colony Stimulating Factor	Amgen (Thousand Oaks, CA)	AIDS, in combination w/AZT
rCD4 Recombinant Soluble Human CD4	Genentech (S. San Francisco,CA)	AIDS, ARC
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen (Cambridge, MA)	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche (Nutley, NJ)	Kaposi's sarcoma AIDS, ARC, in combination w/AZT

Drug Name	Manufacturer	Indication
SK&F106528 Soluble T4	Smith, Kline & French Laboratories (Philadelphia, PA)	HIV infection
Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection
Tumor Necrosis Factor; TNF	Genentech (S. San Francisco, CA)	ARC, in combination w/gamma Interferon

ANTI-INFECTIVES

Drug Name	Manufacturer	Indication
Clindamycin with Primaquine	Upjohn (Kalamazoo, MI)	PCP
Fluconazole	Pfizer (New York, NY)	cryptococcal meningitis, candidiasis

Drug Name	Manufacturer	Indication
Pastille Nystatin Pastille	Squibb Corp. (Princeton, NJ)	prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow (Cincinnati, OH)	PCP
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		antibacterial
Trimethoprim/sulfa		antibacterial
Piritrexim	Burroughs Wellcome (Rsch. Triangle Park, NC)	PCP treatment
Pentamidine isethionate for inhalation	Fisons Corporation (Bedford, MA)	PCP prophylaxis
Spiramycin	Rhone-Poulenc Pharmaceuticals (Princeton, NJ)	cryptosporidial diarrhea
Intraconazole-R51211	Janssen Pharm. (Piscataway, NJ)	histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP

OTHER

Drug Name	Manufacturer	Indication
Recombinant Human Erythropoietin	Ortho Pharm. Corp. (Raritan, NJ)	severe anemia assoc. with AZT therapy
Megestrol Acetate	Bristol-Myers (New York, NY)	treatment of anorexia assoc. w/AIDS
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals (Norwich, NY)	diarrhea and malabsorption related to AIDS

It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the list in the above Table, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS.

Certain compounds of Table C are the following: L-697,661 or '661' is 3-([4,7-dichloro-1,3-benzoxazol-2-yl)methyl]-amino)-5-ethyl-6-methyl-pyridin-2(1H)-one; L-696,229 is 3-[2-(1,3-benzoxazol-2-yl)-ethyl]-5-ethyl-6-methyl-pyridin-2(1H)-one. The synthesis of L-697,661 and L-696,229 is described in EPO 484071, and EPO 462800, both herein incorporated by reference. The synthesis of ddC, ddI and AZT are also described in EPO 484071.

Preferred combinations are simultaneous or alternating treatments of an inhibitor of HIV protease and a non-nucleoside inhibitor of HIV reverse transcriptase. An optional third component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, ddC or ddI.

EXAMPLE 1

Preparation of N-t-butyl-4-(1,1-dimethylethoxycarbonyl)-piperazine-2(S)-carboxamide, Compound 4

Step 1: Preparation of 4-(1,1-dimethylethoxycarbonyl)-1-(phenylmethoxycarbonyl)-piperazine-2(S)-carboxamide

The title compound was prepared following the procedure of Bigge, C.F. et al.; Tetrahderon Lett, 30, 5193 (1989); starting with 2(S)-piperazinecarboxylic acid. (See also Felder, E. et al. ; Helv. Chim. Acta 117, 888 (1960)).

Step 2: Preparation of N-t-butyl-4-(1,1-dimethylethoxy-carbonyl)-1-(phenylmethoxycarbonyl)-piperazine-2(S)-carboxamide

To 9.90 g (27.16 mmol) of 4-(1,1-dimethylethoxycarbonyl)-1-(phenylmethoxycarbonyl)-piperazine-2(S)-carboxamide dissolved in 75 mL of DMF and cooled to 0°C were added 5.73 g (29.88 mmol) of EDC, 4.03 g (29.88 mmol) of HOBt, 3.14 mL (29.88 mmol) of t-butylamine, and finally 4.16 mL (29.88 mmol) of triethylamine. The reaction mixture was stirred for 18 hours and the reaction volume was concentrated under reduced pressure. The residue was then diluted with 600 mL of EtOAc and washed with 10% HCl (2 x 75 mL), saturated $NaHCO_3$ (1 x 75 mL) , water (3 x 75 mL) and brine (1 x 50 mL), dried over $MgSO_4$ and concentrated to a solid. This solid was triturated with EtOAc: hexane (1:2) and filtered to provide the title compound as a white solid; mp 134-135°C.

Step 3: Preparation of N-t-butyl-4-(1,1-dimethylethoxycarbonyl)-piperazine-2(S)-carboxamide

To 1.20 g (2.86 mmol) of N-t-butyl-4-(1,1-dimethyl-ethoxy-carbonyl)-1-(phenylmethylcarbonyl)piperazine-2(S)-carboxamide and 1.1g (0.086 mmol) of 10% Pd/C was added 15 mL of methanol. The vessel was charged with hydrogen and the reaction stirred for 2 hours, filtered through celite and washed with ethanol.

The solvents were removed in vacuo to provide the title product as a foam.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (br, 1H), 4.10 (m, 1H), 3.81 (br, 1H), 3.21 (dd, J=18 and 7 Hz, 1H), 3.02-2.70 (m, 4H), 2.10-2.0 (br, 1H), 1.50 (s, 9H), 1.41(s, 9H).

EXAMPLE 2

Preparation of 3(S)-azido-(1,2R)-epoxy-4-phenylbutane, Compound 9

A quantity of CuCN, 2.43 g, was added to a solution of butadiene monooxide, 19 g, in 500 mL anhydrous tetrahydrofuran and the mixture was cooled to -78°C. Phenyl magnesium bromide solution in ether, 32 mmol, was added dropwise to this mixture. The reaction mixture was warmed to 0°C and was stirred until the reaction became homogeneous. The reaction mixture was cooled to -78°C and 0.29 mole of phenylmagnesium bromide solution in ether was added dropwise for 30 min. The reaction mixture was allowed to warm to room temperature with stirring then quenched by slow addition of saturated NH_4Cl (50 mL) followed by NH_4OH (30 mL), saturated NH_4Cl (200 mL) and H_2O (100 mL). Aqueous layer was extracted with two 200 mL portions of ethyl acetate. Combined organic layers were dried and concentrated. The residue was distilled under vacuum (0.1 torr) at 100°C to give trans-4-phenyl-2-butene-1-ol (38.9 g, 79% pure).

A mixture of powdered 4 Å molecular sieves, 3 g, titanium tetraisopropoxide, 1.5 mL, and diethyl D-tartrate, 1.1 mL, in anhydrous methylene chloride (350 mL) was cooled to -20°C and tertbutylhydroperoxide solution in isooctane, 210 mmol, was added slowly with stirring. After 30 minutes at -20°C a solution of trans-4-phenyl-2-butene-1-ol, 15.3 g, in anhydrous methylene chloride (50 mL) was added dropwise for 20 min at -20°C. The reaction mixture was aged at -20°C in a freezer for 20 hours. Water (40 mL) was added to the reaction mixture and after 30 minutes at 0°C, 30% NaOH in brine (6 mL) was added. The resulting mixture was stirred for 1 h at room temperature. The organic phase was separated and the aqueous layer

was extracted with two 30 mL portions of methylene chloride. Combined organic layers were dried over Na_2SO_4, diluted with toluene (300 mL) and concentrated. Chromatography on silica gel with 40% ethyl acetate in hexane gave (2R, 3R)-epoxy-4-phenylbutan-1-ol, compound 7 (10.3 g).

A solution of titanium tetraisopropoxide, 5.6 mL, and azidotrimethylsilane, 5.0 mL, in anhydrous benzene (100 mL) was refluxed for 5 h. To this refluxing mixture was added a solution of compound 7, 2.6 g, in anhydrous benzene (10 mL). The reaction mixture was refluxed for 15 min, cooled to room temperature and quenched by addition of 5% H_2SO_4 (150 mL). After stirring the resulting biphasic mixture for 1 h, the organic layer was separated and the aqueous layer was extracted with two 20 mL portions of ethyl acetate. Combined organic layers were washed with saturated sodium bicarbonate (50 mL), dried over $MgSO_4$ and concentrated. The oily azidodiol product was dissolved in chloroform (30 mL) and 2-acetoxyisobutyryl chloride, 2.5 mL, was added. After stirring for 5 h at room temperature, saturated sodium bicarbonate (50 mL) was added and the resulting biphasic mixture was stirred for 10 min. The aqueous layer was extracted with two 30 mL portions of chloroform. Combined organic layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in anhydrous tetrahydrofuran (10 mL) and solid NaOMe, 0.614 g, was added. After stirring for 3 h at room temperature, saturated NH_4Cl (20 mL) was added and the mixture extracted with two 20 mL portions of ethyl acetate. Combined organic layers were dried over $MgSO_4$ and concentrated. Chromatography on silica gel with 8% ethyl acetate in hexanes gave 3(S)-azido-(1, 2R)-epoxy-4-phenylbutane (1.32 g) as an oil.

EXAMPLE 3

Preparation of 2(R,S)-(methylethyl)-3(R,S)-hydroxytetrahydro-thiophene, Compound 13

Ethyl 3-mercaptopropionate (22.46 g) was dissolved in absolute ethanol (60 mL) and the solution was cooled to -20°C. To it was added sodium ethoxide solution in ethanol (62.5 mL of 21%). A solution of ethyl 2-bromoisovalerate (35 g) in absolute ethanol (60 mL) was added slowly. The reaction mixture was stirred for 2 hours while the reaction temperature was allowed to warm to room temperature. Saturated NH_4Cl (150 mL) was added to the reaction mixture and organic layer was separated. The aqueous layer was extracted with ethyl acetate (100 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated. Sodium (0.88 g) was dissolved in absolute ethanol (40 mL) at 0°C and the solution was concentrated. The residue was dissolved in toluene and the product from the previous reaction, compound 10, (7.78 g) was added. The reaction mixture was heated to reflux for 2 hours. The reaction mixture was cooled to room temperature and 1N HCl was added to the reaction mixture until the pH became acidic. The crude product was extracted with EtOAc (50 mL x 3) and the combined organic layers were washed with brine, were dried over Na_2SO_4 and concentrated. The residue, compound 11, was heated with 10% H_2SO_4 (40 mL) at 100°C overnight. The crude product was extracted with ethyl acetate (50 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue (2(S,R)-(methylethyl)-tetrahydrothiophen-3-one), compound 12, was dissolved in methylene chloride (60 mL) and the solution was cooled to 0°C. Diisobutylaluminumhydride (25 mL, 1M) in methylene chloride was added dropwise. The reaction mixture was stirred for one hour at 0°C. The reaction was quenched by the dropwise addition of water until no gas evolved. 1N HCl (50 mL) was added and the crude product was extracted with methylene chloride (50 mL x 3). Combined organic layers were washed with saturated $NaHCO_3$, brine and dried over Na_2SO_4. Concentration and purification by column chromatography, eluting with 20% ethyl acetate in hexane gave compound 13, as an oil (1.72 g): ^1H NMR ($CDCl_3$): 4.36 (br, s, 1H), 3.1-2.85 (m, 3H), 2.23 (dd, J=6.8 Hz, 13.3 Hz, 1H), 1.95-1.77 (m, 3H), 1.07 (d, J=6.5 Hz, 3H), 1.02 (d, J=6.7 Hz, 3H).

EXAMPLE 4

Preparation of 3(R,S)-[2(R,S)-methylethyl]tetrahydrothienyl succinimidyl carbonate, Compound 14

A mixture of 1.52 g (10.4 mmol) of 2(R,S)-methylethyl-3(R,S)-hydroxytetrahydrothiophene, 2.93 g (11.4 mmol) of N,N'-disuccinimidyl carbonate and 1.16 g (11.4 mmol) of triethylamine was dissolved in 25 mL of acetonitrile and stirred for 18 hours. The solvent was removed in vacuo and the resulting mixture partitioned between 100 mL of EtOAc and water (1:1). The aqueous layer was separated and washed with water (2 x 50 mL), brine (1 x 60 mL), dried, filtered, and the solvent removed. The resulting solid was dissolved in 100 mL EtOAc/hexane (1:1) and passed through a 3" silica gel pad. The pad was washed with an additional 1 L of EtOAc/hexane and the solvent removed to give 2.8 g (93%) of the desired carbonate.

EXAMPLE 5

Preparation of 3(S)-tetrahydrofuranyl succinimidyl carbonate, Compound 15

A mixture of 3(S)-hydroxytetrahydrofuran (1.91 g), disuccinimidyl carbonate (5.538 g), and triethylamine (3.17 mL) in 20 mL of methylene chloride was stirred for 15 hours. The mixture was washed with 10% aqueous citric acid solution (1 x 15 mL), sat aq $NaHCO_3$ solution (1 x 15 mL), water and brine (1 x 15 mL), and dried over anhyd Na_2SO_4. Filtration followed by removal of the solvent provided 3.865 g of pale yellow solid which was recrystallized from EtOAc/hexane to give white solid (2.654 g, 53%). ^1H NMR ($CDCl_3$) 5.36 (1H, m), 3.87-4.03 (4H, m), 2.85 (4H, s), 2.24 (2H, m).

EXAMPLE 6

Preparation of 3(S)-tetrahydrothienyl succinimidyl carbonate, Compound 16

To a stirred solution of 3(S)-hydroxytetrahydrothiophene, 0.490 g, and disuccinimidyl carbonate, 1.206 g in 3 mL of dry methylene chloride was added 0.688 ml of triethylamine. After stirring for 6 hours, the mixture was diluted with methylene chloride and washed with saturated aqueous $NaHCO_3$ (10 ml) and brine and dried over anhydrous Na_2SO_4. Filtration and concentration under reduced pressure gave a residue (1.035 g, 82%). ^1H NMR ($CDCl_3$) 5.52 (1H, m), 2.75-3.24 (4H, m), 2.84 (4H, s), 2.48 (1H, m), 2.06 (1H, m).

EXAMPLE 7

Preparation of N-tert-butyl-1-[3(S)-azido-2(R)-hydroxy-4-phenylbutyl]-4-(1,1-dimethylethoxycarbonyl)piperazine-2(S)-carboxamide, Compound 17

A mixture of 22.4 g (80 mmol) of N-t-butyl-4-(1,1-dimethylethoxycarbonyl)piperazine-2(S)-carboxamide (product of Example 1) and 15 g (80 mmol) of 3(S)-azido-(1,2R)-epoxy-4-phenylbutane (product of Example 2) in 200 mL of isopropanol was heated to 80°C for 18 hours. Subsequent removal of the solvent under reduced pressure gave 23 g (50 mmol) of the desired product as a resin which was used without further purification in the next step.

Alternatively, a mixture of 0.063 g (0.2 mmol) N-tert-butyl-4-(1,1-dimethylethoxycarbonyl)piperazine-2(S)-carboxamide and 1.6 g (22 mmol) Al_2O_3 in 50 mL Et_2O was stirred for 30 min, after which 0.038 g (0.2 mmol) 3(S)-azido-(1,2(R))-epoxy-4-phenylbutane was added. Stirring was continued for 18 hours, after which the solid was filtered and washed with 50 mL of Et_2O. The filtrate was concentrated to dryness and the residue was purified by preparative thin layer chromatography (5% methanol in methylene chloride) to give 0.055 g (0.012 mmol) of the desired product as a resin in 59% yield.

EXAMPLE 8

Preparation of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[2"'(R)-methylethyl]tetrahydrothienyloxycarbonylamino]butyl]-4-(1,1-dimethylethoxycarbonyl)piperazine-2(S)-carboxamide, Compound 19

A mixture of 23 g N-tert-butyl-1-[3(S)-azido-2(R)-hydroxy-4-phenylbutyl]-4-(1,1-dimethylethoxycarbonyl)piperazine-2(S)-carboxamide and 2 g of $Pd(OH)_2/C$ in 100 mL ethanol was shaken under a hydrogen atmosphere at ambient pressure for 18 hours. The solid was filtered through a Celite pad and washed with 50 mL of ethanol. The solvent was removed under reduced pressure and the residue partitioned between 200 mL ethyl acetate/water (1:1). The aqueous layer was separated and washed with EtOAc (1 x 20 mL). The combined organic layer was washed with water (2 x 50 mL) and brine (1 x 60 mL), dried, and the solvent removed to yield 19 g of crude amine which (Compound 18) which was used without further purification.

To a stirred solution of 0.100 g (0.23 mmol) of N-tert-butyl-1-[3(S)-amino-2(R)-hydroxy-4-phenylbutyl]-4-(1,1-dimethylethoxycarbonyl)piperazine-2(S)-carboxamide (Compound 18) and 0.066 g (0.023 mmol) of 3(R,S)-[2(R,S)-methylethyl]-tetrahydrothienyl succinimidyl carbonate (product of Example 4) in 2 mL of methylene chloride was added 0.023 g (0.032 mL, 0.23 mmol) of triethylamine and the stirring was continued for 15 hours at ambient temperature. The mixture was partitioned between water (5 mL) and methylene chloride (5 mL) and the aqueous layer was extracted with methylene chloride (3 x 5 mL). Combined organic layer was washed with water (5 mL) and brine (5 mL) and dried over anhyd. Na_2SO_4. Removal of solvent in vacuo followed by preparative thin layer chromatography (silica gel, 20 x 20 cm, 1 mm, 5% $MeOH/CH_2Cl_2$) provided 0.101 g (71% yield) of a diastereomeric mixture as a gummy residue. UV(λmax)=256 nm; ^1H NMR ($CDCl_3$): 7.18-7.30 (5H, m), 6.20 (1H, br s), 5.24 (1H, d, J=9 Hz), 4.94 (1H, m), 1.6-4.0 (20 H),

1.44 (9H, s), 1.35 (9H, s), 0.96 (3/2H, d, J=7 Hz), 0.95 (3/2H, d, J=7 Hz), 0.93 (3/2H, d, J=7 Hz), 0.86 (3/2H, d J=7 Hz).

EXAMPLE 9

Preparation of N-tert-butyl-1-[3'(S)-[3"(S)-tetrahydrofuranyloxy-carbonylamino]-2'(R)-hydroxy-4'-phenylbutyl]-4-(3'-hydroxy-phenylmethyl)piperazine-2(S)-carboxamide, Compound B

To a stirred solution of N-tert-butyl-1-[3'(S)-[3"(S)-tetrahydrofuranyloxycarbonylamino]-2'(R)-hydroxy-4'-phenyl-butyl]piperazine-2(S)-carboxamide (25 mg) and 3-hydroxybenzaldehyde (9.9 mg) in methanol (0.5 mL) and THF (0.1 mL) were added $NaB(CN)H_3$ (5.1 mg), and AcOH (3.7 μL). The mixture was stirred for 15 hours and 10% aq citric acid (1 mL) was added. Stirring was continued for 30 min and sat aq $NaHCO_3$ solution (3 mL) was added. The mixture was diluted with $CHCl_3$ (10 mL) and layers separated. The aqueous layer was extracted with chloroform (2 x 5 mL) and the combined organic layer was washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was then purified on a preparative thin layer chromatography (5% methanol-CH_2Cl_2) to provide 19 mg (62%) of the desired product. mp 88-91°C, UV(λmax)=278 nm, ^1H NMR ($CDCl_3$) 8.24 (1H, br s), 6.77 -7.31 (5H, m), 5.21 (1H, d J=3 Hz), 5.10 (1H, m), 3.70-3.94 (m), 3.31-3.60 (m), 2.55-2.96 (m), 2.46 (1H, m), 2.32(1H, m), 2.06 (1H, m), 1.92 (1H, m), 1.37 (9H, s),

Elemental analysis, calc'd. for $C_{31}H_{44}N_4O_6$ x 0.25 $CHCl_3$ (592.60):

C, 63.23; H, 7.52; N, 9.46

Found: C, 63.29; H, 7.65; N, 9.33

EXAMPLE 10

Preparation of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxycarbonylamino]-butyl]-4-(1',1'-dimethylethoxycarbonyl)piperazine-2(S)-carboxamide

To a stirred solution of 50 mg (0.08 mmol) of a 1:1 mixture of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[2"'(R)-methylethyl]tetrahydrothienyloxy-carbonylamino]butyl]-4-(1',1'-dimethylethoxycarbonyl)piperazine-2(S)-carboxamide and N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(S)-[2"'(S)-methylethyl]-tetrahydrothienyloxy-carbonylamino]butyl]-4-(1',1'-dimethylethoxy-carbonyl)piperazine-2(S)-carboxamide, 28 mg (0.24 mmol) of N-methylmorpholine N-oxide were stirred in 0.5 mL 10:1 acetone water was added 0.1 ml OsO_4 solution in t-butanol (2.5%). After stirring 18 hours, 0.5 g sodium metabisulfite was added and stirring was continued for 30 min. The solid was filtered and the solvent removed. The residue was partitioned between 50 mL 1:1 EtOAc/water, the organic layer separated and the aqueous washed with EtOAc (2 x 20 mL). The combined organics were then washed with water (3 x 25 mL), brine (1 x 30 mL), dried, and the solvent removed. Medium pressure silica gel liquid chromatography (1:1 hexane/EtOAc) of the residue yielded 19.2 mg of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxycarbonyl-amino]butyl]-4-(1',1'-dimethylethoxycarbonyl)piperazine-2(S)-carboxamide, the desired compound, as the first fraction and 19.5 mg of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(S)-[1"',1"'-dioxo-2"'(S)-methylethyl]tetrahydrothienyloxycarbonylamino]butyl]-4-(1',1'-dimethylethoxycarbonyl) piperazine-2(S)-carboxamide as the second fraction. UV (λmax) = 258 nm, ^{1}H NMR ($CDCl_3$) 7.14-7.35 (5H, m), 6.17 (1H, m), 5.26 (2H, m), 3.94 (1H, m), 3.83 (1H, m), 3.71 (1H, m), 3.24-3.64 (3H, m), 2.30-3.24 (9H, m), 2.17 (1H, m), 1.96 (1H, m), 1.07-1.80 (5H, m), 1.47 (9H, s), 1.31 (9H, s), 1.15 (3H, d, J=10 Hz), 0.94 (3H, d, J=10 Hz). Elemental Analysis, calc'd for $C_{32}H_{52}N_4O_8S$ x 0.55 $CH_3COOC_2H_5$ + 0.65 CH_2Cl_2 (M.W.=756.526):

C, 55.33; H, 7.69; N. 7.41

Found: C, 55.38; H, 7.45; N, 7.40

EXAMPLE 11

Preparation of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxy-carbonyl-amino]butyl]piperazine-2(S)-carboxamide, Compound 20

HCl gas was bubbled through a stirred solution of 1 g of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxy-carbonylamino]butyl]-4-(1',1'-dimethylethoxycarbonyl) piperazine-2(S)-carboxamide in 50 mL EtOAc at 0°C for 10 min., after which the gas flow was stopped and the reaction mixture allowed to stir for an additional 15 min. The solvent was removed under reduced pressure and the residue treated with 50 mL $CHCl_3$ which had been previously saturated with NH_3 gas. The resulting slurry was filtered and the solvent removed in vacuo to give 0.8 g N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydro-thienyloxycarbonylamino]butyl]-piperazine-2(S)-carboxamide as a resin.

EXAMPLE 12

Preparation of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxycarbonylamino]-butyl]-4-[4'-(2"-chloro-6"-methyl)pyridylmethyl]piperazine-2(S)-carboxamide, Compound E

A mixture of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyl-oxycarbonylamino]butyl]piperazine-2(S)-carboxamide (0.482 g), HCl salt of 4-(2-chloro-6-methyl)pyridylmethyl chloride (0.205 g), and triethylamine (0.365 mL) in DMF (5 mL) was stirred for 18 h. The mixture was diluted with 250 mL of EtOAc and washed with water (3 x 12 mL), brine (1 x 10 mL), dried over anhyd $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with NH_3 saturated chloroform) to give 401 mg of white solid after removal of residual DMF. m.p. 102-107°C; ^1H NMR ($CDCl_3$): 7.87 (1H, br s), 7.18-7.27

(5H, m), 7.10 (1H, s), 7.00 (1H, s), 5.39 (1H, m), 5.25 (1H, m), 3.89-3.93 (2H, m), 3.40-3.46 (2H, m), 3.07 (1H, dd, J=5.0, 12.8), 2.28-3.00 (13H, m), 2.53 (3H, s), 2.39 (1H, m), 2.17 (1H, m), 1.88-2.00 (1H, m), 1.64-1.81 (1H, br s), 1.40 (9H, s), 1.17 (3H, d, J=6.4), 0.93 (3H, d, J=6.7).

Elemental analysis calculated for $C_{34}H_{50}N_5O_6SCl + 0.15\ CHCl_3$ (710.233):

C, 57.75; H, 7.12; N, 9.86

Found: C, 57.56; H, 6.86; N, 9.49

EXAMPLE 13

Preparation of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxycarbonylamino]-butyl]-4-(3'-quinolinylmethyl)piperazine-2(S)-carboxamide,

Compound F

A mixture of 0.055 g (0.1 mmol) N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)methylethyl]-tetrahydrothienyloxycarbonylamino]butyl]piperazine-2(S)-carboxamide, 0.018 g (0.1 mmol) of 3-chloromethylquinoline and 0.01 g (0.1 mmol) triethylamine in 5 mL DMF was stirred for 18 hours. Removal of the solvent in vacuo followed by workup and purification by preparative thin layer chromatography (10% methanol in NH_3 sat. $CHCl_3$) yielded 0.04 g (0.057 mmol, 58%) N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyl-oxycarbonylamino]butyl]-4-(3'-quinolinylmethyl)piperazine-2(S)-carboxamide as an amorphous solid. m.p.119-121°C; UV (λmax) 227 nm; ^1H NMR ($CDCl_3$) 8.84 (1H, s), 8.14 (1H, d, J=12 Hz), 7.83 (1H, d, J=12 Hz), 7.77 (1H, t, J=10 Hz), 7.60 (1H, t, J=10 Hz), 7.15-7.33 (5H, m), 5.32 (2H, s), 3.94 (2H, m), 3.79 (2H, m), 2.49-3.28 (14H, m), 2.19 (2H, m), 1.99 (2H, m), 1.37 (9H, s), 1.18 (3H, d, J=12 Hz), 0.95 (3H, d, J=12 Hz).

Elemental anlysis, calc'd for $C_{37}H_{51}N_5O_6S$ x $CH_3COOC_2H_5$ (M.W.=693.90):

C, 62.97; H, 7.60; N, 8.96
Found: C, 63.09; H, 7.61; N, 8.93

EXAMPLE 14

Preparation of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxycarbonylamino]-butyl]-4-(3'-hydroxyphenylmethyl)piperazine-2(S)-carboxamide, Compound C

A mixture of 0.018 g (0.032 mmol) N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]-tetrahydrothienyloxycarbonylamino]butyl]piperazine-2(S)-carboxamide, 0.004 g (0.032 mmol) 3-hydroxybenzaldehyde and 0.002 g (0.032 mmol) sodium cyanoborohydride was dissolved in 2 mL methanol and the pH adjusted to 6.0 by the addition of glacial acetic acid. After stirring 18 hours, 2 mL 10% citric acid was added and the reaction mixtue stirred for an additional 30 min, after which the methanol was removed under reduced pressure and the residue partitioned between 20 mL EtOAc/ sat aq sodium bicarbonate solution (1:1). The layers were separated and the aqueous layer was washed with additional ethyl acetate. The combined organics were washed with brine, dried, and the solvent removed. Further purification by preparative thin layer chromatography (silica gel, 10% methanol in ethyl acetate) gave 0.011 g (52%) as a resin. m.p. 131-133°C; UV (λmax)=279 nm; ^{1}H NMR ($CDCl_3$) 7.22 (8H, m), 6.91 (1H, m), 6.81 (1H, m), 5.69 (1H, m), 5.21 (1H, s), 3.60-4.28 (4H, m), 2.24-3.37 (12H, m), 1.43-2.23 (7H, m), 1.30 (9H, s), 1.14 (3H, d, J=12 Hz), 0.094 (3H, d, J=12 Hz). Elemental analysis, calc'd for $C_{34}H_{50}N_4O_7S \times CH_3COOC_2H_5$ (M.W.=746.974):

C, 61.10; H, 7.83: N, 7.50
Found: C, 61.38; N, 7.82: N, 7.58

EXAMPLE 15

Preparation of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxycarbonylamino]-butyl]-4-(4'-pyridylmethyl)piperazine-2(S)-carboxamide, Compound D

To a solution of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxy-carbonylamino]-butyl]piperazine-2(S)-carboxamide (0.812 g, 1.47 mmol) in 3 mL DMF was added 4-chloromethylpyridine (0.375 g, 2.94 mmol) followed by triethylamine (0.61 mL, 4.38 mmol). After stirring at room temperature for 18 hrs, the solvent was removed in vacuo and the resulting residue partitioned between 100 mL ethyl acetate/ 100 mL water. The water layer was separated and the organic layer washed with 2 x 100 mL water and 1 x 150 mL brine. After drying (Na_2SO_4) and filtering, the solvent was removed in vacuo to obtain the crude product, which was purified by column chromatography (silica gel, 1.5-5.0% MeOH/NH_3 sat $CHCl_3$) to give 0..431 g (46% yield) of the pure product. m.p. 93-98°C; UV (λmax)=255 nm; ^{1}H NMR ($CDCl_3$) 8.60 (2H, m), 7.18-7.36 (7H, m), 5.32 (1H, d, J=8 Hz), 5.29 (1H, m), 3.96 (2H, m), 3.58 (2H, m), 2.4-3.12 (13H, m), 2.20 (1H, m), 2.00 (2H, m), 1.40 (9H, s), 1.22 (3H, d, J=5 Hz), 0.98 (3H, d, J=5 Hz). Elemental Analysis calc'd for $C_{33}H_{49}N_5O_6S$ x 0.15 $CHCl_3$ (661.76):

C, 60.17; H, 7.49; N, 10.58

Found C, 59.98; H, 7.51; N, 10.19

EXAMPLE 16

Preparation of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxycarbonylamino]-butyl]-4-(2'-thienylmethyl)piperazine-2(S)-carboxamide, Compound G

To a solution of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxy-carbonylamino]butyl]piperazine-2(S)-carboxamide (0.055 g, 0.1 mmol) and thiophene-2-carboxaldehyde (0.011 g, 0.1 mmol) in 1.0 mL

methanol was added sodium cyanoborohydride (0.007 g, 0.1 mmol) and the pH of the mixture was adjusted to 6.0 with acetic acid. The mixture was stirred 18 h at room temperature and 1 mL 10% aqueous citric acid solution was added and stirring was continued for 30 min. Methanol was removed in vacuo and the residue was partitioned between EtOAc (10 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (10 mL) and organic layers combined. Combined organic layers were washed with water (5 mL) and brine (5 mL) and dried over anhyd. sodium sulfate. Filtration followed by removal of solvent under reduced pressure gave a residue which was purified on a preparative thin layer chromatography (5% MeOH/NH_3 sat. $CHCl_3$) to yield 0.041 g (66% yield) of the desired product as a glass. m.p. 104-106°C; UV(λmax) 231 nm; ^{1}H NMR ($CDCl_3$) 8.21 (1H, br s), 7.16-7.32 (6H, m), 6.96 (2H, m), 5.35 (1H, d, J=8 Hz), 5.22 (1H, m), 3.80-3.96 (2H, m), 3.60-3.75 (2H, m), 3.42 (1H, m), 1.82-3.10 (17H, m), 1.39 (9H, s), 1.18 (3H, d, J=5 Hz), 0.94 (3H, d, J=5 Hz). Elemental Analysis calc'd for $C_{32}H_{48}N_4O_6S$ x 0.4 $CHCl_3$ and 0.85 CH_3OH (691.816)

C, 57.72; H, 7.55; N, 8.10

Found C, 57.68; H, 7.34; N, 7.70

EXAMPLE 17

Preparation of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxy-carbonyl-amino]butyl]-4-(2'-thieno[2,3-b]thienylmethyl)piperazine-2(S)-carboxamide, Compound H

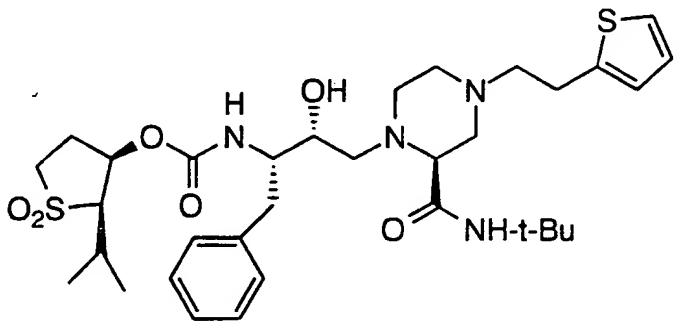
To a solution of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxy-carbonylamino]butyl]piperazine-2(S)-carboxamide (0.5 g, .91 mmol) in 10 mL DMF was added 2-chloromethylthieno[2,3-*b*]thiophene (0.163 g, .91 mmol) followed by triethylamine (0.091 g, 0.127 mL, 0.91 mmol). After stirring at ambient temperature for 18 hours, the solvent was removed in vacuo and the resulting residue partitioned between 100 mL ethyl acetate/100 mL water. The water layer was separated and the organic layer washed with 2 x 100 mL water and 1 x 150 mL brine.

After drying (Na_2SO_4) and filtering, the solvent was removed in vacuo to obain the crude product, which was purified by medium pressure column chromatography (5% MeOH/NH_3 saturated $CHCl_3$) to give 0.312 g (0.44 mmol, 49% yield) of the pure product. m.p. 113-115°C; UV (λmax)= 229 n; ^{1}H NMR ($CDCl_3$) 8.11 (1H, br s), 7.09-7.38 (8H, m), 5.37 (1H, d, J=7 Hz), 5.23 (1H, m), 3.84-3.96 (4H, m), 3.42 (1H, m), 2.50-3.05 (14 H), 2.30 (1H, m), 2.19 (1H, m), 1.96 (1H, m), 1.42 (9H, s), 1.18 (3H, d, J=5 Hz), 0.93 (3H, d, J=5 Hz). Elemental Analysis calculated for $C_{34}H_{48}N_4O_6S_3$ x 0.35 $CH_3COOCH_2CH_3$ (735.816)

C, 57.78; H, 6.96; N, 7.61

Found C, 57.38; H, 6.73; N, 7.60

EXAMPLE 18



Preparation of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxy-carbonyl-amino]butyl]-4-(2'-(2-thienyl)ethyl)piperazine-2(S)-carboxamide

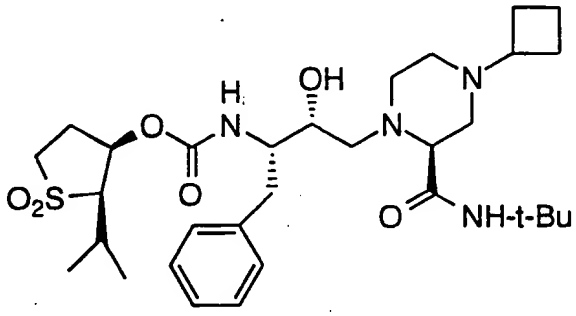
To a solution of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyl-oxycarbonylamino]butyl]piperazine-2(S)-carboxamide (0.020 g, 0.0362 mmol, Example 11) and 2-thienylethanal (0.007 g, 0.0507 mmol) in 0.3 mL 1,2-dichloroethane were added sodium triacetoxyborohydride (0.011 g, 0.0507 mmol) and acetic acid (0.0026 g, 0.0434 mmol). The mixture was stirred 18 h at room temperature and was directly purified by preparative silica gel thin layer chromatography (20 x 20 cm, 1 mm, 5% MeOH/NH_3 sat. $CHCl_3$) to yield 0.022 g (92% yield) of the desired

product as a white solid. UV(lmax) 231 nm. m.p. 103-106°C. ^1H NMR ($CDCl_3$) 8.28 (1H, br s), 7.16-7.30 (6H, m), 6.93-6.98 (2H, m), 5.23-5.31 (2H, m), 3.84-3.92 (2H, m), 3.70 (2H, m), 3.43 (1H, m), 2.61-3.12 (12H, m), 2.45 (1H, dd, J=3.4, 11.5 Hz), 2.12-2.30 (2H, m), 1.85-1.99 (2H, m), 1.41 (9H, s), 1.27 (2H, t, J=7.2 Hz), 1.17 (3H, d, J=6.5 Hz), 0.92 (3H, d, J=6.6 Hz), Elemental Analysis calc'd for $C_{32}H_{48}N_4O_6S$ x 0.2 $CHCl_3$ (752.176)

C, 58.06; H, 7.37; N, 8.16

Found C, 58.11; H, 7.30; N, 8.21

EXAMPLE 19



Preparation of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxy-carbonyl-amino]butyl]-4-cyclobutylpiperazine-2(S)-carboxamide

To a solution of N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxy-carbonylamino]butyl]piperazine-2(S)-carboxamide (0.325 g, 0.588 mmol, Example 11) and cyclobutanone (0.062 g, 0.882 mmol) in 2.0 mL 1,2-dichloroethane were added sodium triacetoxyborohydride (0.174 g, 0.823 mmol) and acetic acid (0.042 g, 0.706 mmol). The mixture was stirred 18 h at room temperature and was partitioned between EtOAc (20 mL) and sat aq $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with EtOAc (10 mLx2) and organic layers combined. The combined organic layers were washed with water (10mL), brine (10 mL), and were dried over anhydrous sodium sulfate.

Filtration, followed by removal of solvent under reduced pressure, gave a residue that was purified via silica gel column chromatography (2% MeOH/NH_3 sat. $CHCl_3$) to yield 0.310 g (87% yield) of the desired product as a glass. UV(lmax) 245 nm. m.p. 97-101°C. ^1H NMR ($CDCl_3$) 9.01 (1H, br s), 7.14-7.27 (5H, m), 5.18-5.23 (2H, m), 3.83-3.94 (2H, m), 3.40 (1H, m), 3.04-3.09 (1H, m), 2.58-2.98 (12H, m), 1.71-2.21 (11H, m), 1.40 (9H, s), 1.17 (3H, d, J=6.4 Hz), 0.92 (3H, d, J=6.6 Hz), Elemental Analysis calc'd for $C_{32}H_{48}N_4O_6S$ x 0.2 $CHCl_3$ (630.709)

C, 59.41; H, 8.02; N, 8.88

Found C, 59.62; H, 8.12; N, 8.50

EXAMPLE 20

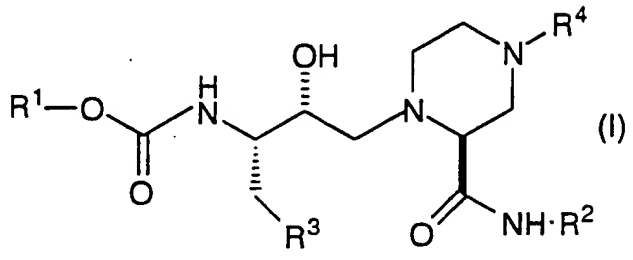
Assay for Inhibition of Microbial Expressed HIV Protease

Inhibition studies of the reaction of the protease expressed in Escherichia coli with a peptide substrate [Val-Ser-Gln-Asn-(betanaphthyl)Ala-Pro-Ile-Val, 0.5 mg/mL at the time the reaction is initiated] were in 50 mM Na acetate, pH 5.5, at 30°C for 1 hour. Various concentrations of inhibitor in 1.0 ul DMSO were added to 25 ul of the peptide solution in water. The reaction is initiated by the addition of 15 ul of 0.33 nM protease (0.11 ng) in a solution of 0.133 M Na acetate pH 5.5 and 0.26% bovine serum albumin. The reaction was quenched with 160 ul of 5% phosphoric acid. Products of the reaction were separated by HPLC (VYDAC wide pore 5 cm C-18 reverse phase, acetonitrile gradient, 0.1% phosphoric acid). The extent of inhibition of the reaction was determined from the peak heights of the products. HPLC of the products, independently synthesized, proved quantitation standards and confirmation of the product composition. Compounds A-H showed IC_{50} values ranging 0.1 - 20 nM.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations, or modifications, as come within the scope of the following claims and its equivalents.

WHAT IS CLAIMED IS:

1. A compound of the formula



(I)

wherein:

R^1 is
a) 5- to 7-membered carbocylic ring which is either saturated, partially saturated or unsaturated, the carbocylic ring being unsubstituted or substituted with one or more of C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-3} alkoxy, halo-C_{1-3} alkyl, aryl-C_{1-3} alkyl, or C_{3-5} cycloalkyl; or
b) 5- to 7-membered heterocycle having one heteroatom selected from O or S, any of which heterocycle is unsubstituted or substituted with one or more of C_{1-4} alkyl, C_{2-4} alkenyl, oxo, C_{3-5} cycloalkyl, or C_{1-3} alkoxy;

R^2 is
a) C_{1-5} alkyl, unsubstituted or substituted with one or more of -OH or C_{1-3} alkoxy; or
b) 5- to 7-membered carbocyclic ring which is either saturated, partially saturated or unsaturated, the carbocyclic ring being unsubstituted or substituted with one or more of C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-3} alkoxy, or hydroxy;

R^3 is
a) Phenyl unsubstituted or substituted with one or more of -OH or C_{1-3} alkoxy; or

b) C_{5-7} cycloalkyl, unsubstituted or substituted with one or more of -OH or C_{1-3} alkoxy;

R^4 is

a) -V-R^5; wherein V is absent, -C(O)-Q-, or -SO_2-Q-; and wherein Q is absent, -O-, -NH-, or 5- to 7-membered heterocycle, which heterocycle is unsubstituted or substituted with one or more of -C_{1-4}alkyl or halo;

b) 5- to 7- membered heterocycle, unsubstituted or substituted with one or more of -C_{1-4}alkyl or halo;

c) C_{1-4}alkenyl, unsubstituted or substituted once with aryl or heterocycle; or

d) -C_{3-5}cycloalkyl, unsubstituted or substituted at the 3-position with C_{1-4}alkyl;

R^5 is

a) hydrogen, or

b) -C_{1-4}alkyl unsubstituted or substituted with one or more of

i) halo,

ii) hydroxy,

iii) C_{1-3} alkoxy,

iv) aryl unsubstituted or substituted with one or more of C_{1-4}alkyl, C_{1-4}alkoxy, nitro, amino, amido, carboxy hydroxy, halo or aryl;

v) -W-aryl or -W-benzyl, wherein W is -O-, -S-, or -NH-;

vi) heterocycle, unsubstituted or substituted with one or more of C_{1-4}alkyl, hydroxy or halo; or

vii) carboxyl;

c) -C_{3-5}cycloalkyl, unsubstituted or substituted at the 3-position with C_{1-4}alkyl;

or pharmaceutically acceptable salt or hydrate thereof.

2. A compound according to Claim 1, wherein:

R^1 is a 5- to 7-membered heterocycle having one heteroatom selected from 0 or S, any of which heterocycle is unsubstituted or substituted with one or more of C_{1-4} alkyl, C_{2-4} alkenyl, oxo, or C_{1-3} alkoxy;

R^2 is C_{1-5} alkyl, unsubstituted or substituted with one or more of -OH;

R^3 is phenyl unsubstituted or substituted once with -OH or C_{1-3} alkoxy;

R^4 is

a) -V-R^5; wherein V is absent or -SO_2-Q-; and wherein Q is absent or a 5- to 7-membered heterocycle, which heterocycle is unsubstituted or substituted with one or more of -C_{1-4}alkyl or halo; or

b) 5- to 7-membered heterocycle, unsubstituted or substituted with one or more of -C_{1-4}alkyl or halo;

c) -C_{3-5}cycloalkyl, unsubstituted or substituted at the 3-position with C_{1-4}alkyl;

R^5 is -C_{1-4} alkyl unsubstituted or substituted with one or more of

i) aryl unsubstituted or substituted with one or more of C_{1-4} alkyl, hydroxy, halo or aryl; or

ii) heterocycle unsubstituted or substituted with one or more of C_{1-4} alkyl, hydroxy, or halo.

3. A compound according to Claim 2, wherein:

R^1 is 1,1-dioxo-tetrahydrothienyl or tetrahydrofuranyl, either of which is unsubstituted or substituted with C_{1-4} alkyl, C_{2-4} alkenyl or C_{1-3} alkoxy;

R^2 is t-butyl or 2-methylpropyl;

R^3 is phenyl;

R^4 is
a) -V-R^5, wherein V is absent; or
b) 5- to 7-membered heterocycle, unsubstituted or substituted with one or more of -C_{1-4} alkyl or halo.

4. A compound according to Claim 3,
wherein:

R^1 is tetrahydrofuran-3-yl; or,
1,1-dioxo-tetrahydrothien-3-yl, unsubstituted or substituted with methyl, ethyl, n-propyl, i-propyl, methoxy, ethoxy, or propenyl.

5. A compound according to Claim 1,
wherein:

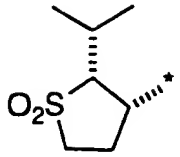
R^1 is a 5- to 7-membered heterocycle having one S heteroatom, said heterocycle unsubstituted or substituted with one or more of C_{1-4} alkyl, oxo or C_{3-5} cycloalkyl;
R^2 is C_{1-5} alkyl;
R^3 is phenyl.

6. A compound according to Claim 5,
wherein:

R^1 is 1,1-dioxotetrahydrothien-3-yl, unsubstituted or substituted with C_{1-4} alkyl, or C_{3-5} cycloalkyl;
R^2 is C_{1-5} alkyl;
R^3 is phenyl.

7. A compound of Claim 1, wherein:

R^1 is



; wherein the asterisk indicates the point of attachment;

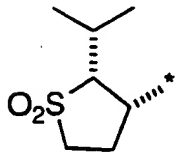
R^2 is t-butyl;

R^3 is phenyl;

R^4 is 4-pyridylmethyl, unsubstituted or substituted at the 2-position with methyl, ethyl, propyl, butyl or isobutyl; C_{3-5} cycloalkyl methyl, unsubstituted or substituted once at the 3-position either with C_{1-4}alkyl.

8. A compound according to Claim 1, wherein:

R^1 is



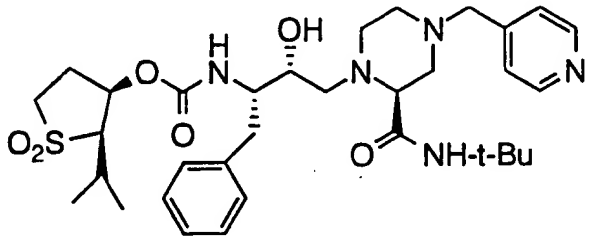
; wherein the asterisk indicates the point of attachment;

R^2 is t-butyl;

R^3 is phenyl;

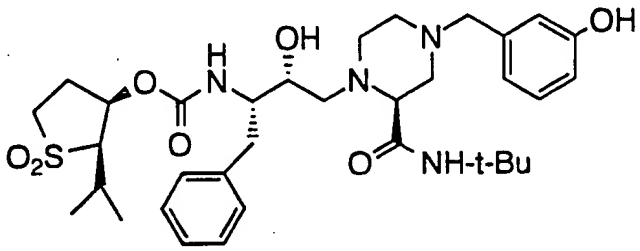
R^4 is methyl, unsubstituted once with imidazopyrazinyl, oxazolopyridinyl, imidazopyridinyl, purinyl, or methylpurinyl.

9. The compound,



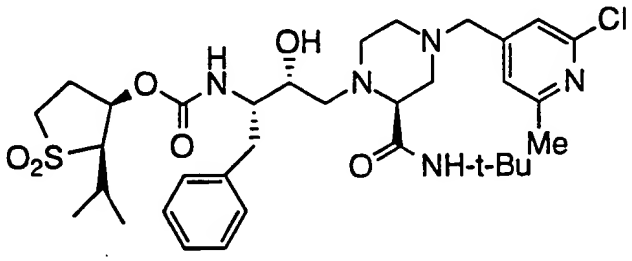
named, N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxycarbonylamino]butyl]-4-(4'-pyridylmethyl)piperazine-2(S)-carboxamide, or pharmaceutically acceptable salt thereof.

10. The compound,



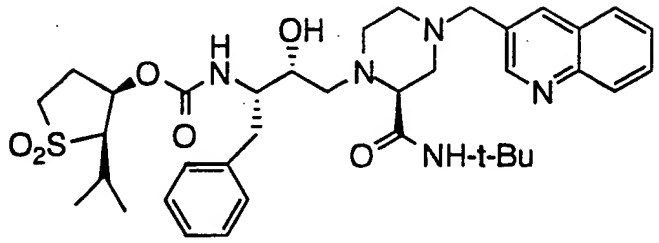
named, N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxycarbonylamino]butyl]-4-(3'-hydroxyphenylmethyl)piperazine-2(S)-carboxamide, or pharmaceutically acceptable salt thereof.

11. The compound,



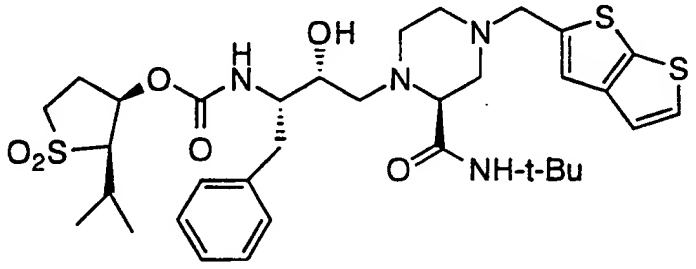
named, N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxycarbonylamino]butyl]-4-[4'-(2"-chloro-6"-methyl)pyridylmethyl]piperazine-2(S)-carboxamide, or pharmaceutically acceptable salt thereof.

12. The compound,



named, N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxycarbonylamino]butyl]-4-(3'-quinolinylmethyl)pyridylmethyl]piperazine-2(S)-carboxamide, or pharmaceutically acceptable salt thereof.

13. The compound,



named, N-tert-butyl-1-[2'(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1"',1"'-dioxo-2"'(R)-methylethyl]tetrahydrothienyloxycarbonylamino]butyl]-4-(2'-thieno[2,3-b]thienylmethyl)piperazine-2(S)-carboxamide, or pharmaceutically acceptable salt thereof.

14. Pharmaceutical composition, for use in the treatment of AIDS, in the prevention of infection by HIV, in the treatment of infection of HIV, or in the inhibition of HIV protease, comprising an effective amount of a compound as in any of Claims 1-13, and a pharmaceutically acceptable carrier.

15. A method of treating AIDS, comprising administering an effective amount of a compound as in any Claims 1-13.

16. A method of preventing infection by HIV, comprising administering an effective amount of a compound as in any of Claims 1-13.

17. A method of treating infection by HIV, comprising administering an effective amount of a compound as in any of Claims 1-13.

18. A method of inhibiting HIV protease, comprising administering an effective amount of a compound as in any of Claims 1-13.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/01370

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07D 401/14, 405/12, 405/14, 409/12; A61K 31/495

US CL :514/252, 253, 255; 544/355, 357, 363, 364, 373, 374, 376, 377

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/252, 253, 255; 544/355, 357, 363, 364, 373, 374, 376, 377

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE STRUCTURE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim N .
A	US, A, 5,157,041 (HANDA et al) 20 October 1992. See claims.	1-18
A	US, A, 5,164,388 (DE et al) 17 November 1992. See column 141 and the claims.	1-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date f the actual completi n of the international search
21 APRIL 1994

Date f mailing of the international search report
MAY 10 1994

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